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CONGO RED IN THE TREATMENT OF PERNICIOUS ANEMIA AND SPRUE.

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In 1933, Massa and Zolezzi,[6a] at the University of Parma Medical Clinic, announced the successful treatment of 2 cases of pernicious anemia with intravenously administered Congo red. A year later they reported favorable results in a larger series of cases.[6b] In 1935, Mermod and Dock[5] apparently confirmed the observations of the Italian authors. Since Congo red is a synthetic colloidal dye with a known chemical formula, it seemed most important to test further the use of this compound in the treatment of pernicious anemia.

Massa and Zolezzi employed a 0.5% solution of Congo red (Grübler) made up in 0.5% saline solution. This solution was warmed almost to boiling, allowed to stand 24 hours, and then filtered through paper. The filtrate was placed in ampules and sterilized by autoclaving for 10 minutes at ¾ to 1 atmosphere. Injections of 20 cc. of this solution were given every 1 to 2 days for 5 to 6 days followed by a rest period of several days. Of fifteen cases treated with Congo red, as far as can be ascertained from the brief case reports, the majority satisfied the usual criteria for the diagnosis of pernicious anemia, *i. e.*, a macrocytic hyperchromic anemia, hyperbilirubinemia, and achylia gastrica. Of the 15 cases, 3 may be dismissed at once as they were given a short course of liver therapy prior to the injections of Congo red. The authors felt that the continued improvement on Congo red pointed to a specific therapeutic effect of the dye; however, as it is well

established that small amounts of liver may produce complete and prolonged remissions in pernicious anemia, it would be impossible to evaluate the efficacy of Congo red in these 3 cases. Of the remaining 12 treated with Congo red alone, 9 had complete blood remissions, whereas 3 failed to respond at all. After receiving a fair trial of the dye, these latter 3 were treated energetically with liver extract to which they responded favorably. Reticulocytes were followed in 5 of the 9 cases which showed remissions on Congo red alone; in these 5 cases reticulocyte peaks of 10 to 25% occurred after the eighth or ninth injection. All of the patients treated successfully with Congo red remained clinically well for the several months of observation following treatment. In an attempt to explain the therapeutic effect of Congo red, Massa and Zolezzi suggested that the dye prevented hemolysis by blocking the reticulo-endothelial cells.

Mermod and Dock reported that they had confirmed the results of Massa and Zolezzi by successfully treating 2 cases of mild pernicious anemia with intravenous Congo red. These authors employed a 1.5% solution of the dye in 6% glucose solution. One patient received 60 cc. of this solution in 5 days, the other 90 cc. in 10 days. Both patients showed a rise in reticulocytes and a fall in serum bilirubin. As soon as the reticulocyte peak was passed, the treatment was changed to liver extract. It is therefore open to question whether complete blood remissions would have followed the reticulocyte crises if Congo red therapy had been continued. Mermod and Dock point to the fact that Congo red is notably effective in neutralizing a variety of toxins and suggest that "in pernicious anemia the dye assists in the detoxification of substances, probably enterogenous in origin, which are hemolytic."

A brief abstract of the results obtained in the treatment of pernicious anemia with Congo red at our clinic has recently appeared.[1] It is the purpose of the present report to give these results in more detail with some additional data.

Because of the difficulty in obtaining suitable cases of pernicious anemia in relapse, the problem was at first attacked from a somewhat different angle. Proven cases of pernicious anemia, which were in a remission as the result of liver extract therapy, were selected from the outpatient clinic. Weekly intravenous injections of Congo red (Grübler) solution were substituted for intramuscular liver extract injections.* A 0.5% solution of the dye in 0.5% saline, prepared exactly according to the method of Massa and Zolezzi, was employed in all cases. Only patients without evidence of combined system disease were selected. Six such patients were treated with Congo red for periods varying from 9 weeks to 6 months. The blood changes

* Liver Extract Lilly N.N.R. was used throughout this study. The solution for intramuscular injection was made up so that 1 cc. of solution contained the amount of extract derived from 5 gm. of whole liver.

are illustrated by Charts I to VI and summarized in Table 1. It is evident that 5 of the 6 patients in this group evinced a marked tendency to relapse as shown by falling red count and hemoglobin as well as by rising mean corpuscular volume and color index. In 4 of the cases distinct symptoms of relapsing pernicious anemia appeared concomitant with the characteristic blood changes. The symptoms disappeared rapidly and the blood levels soon returned to normal when intramuscular liver extract therapy was resumed. These relapses during Congo red therapy are the more significant in that no attempt was made to control the diets of these patients, who had been previously trained to eat plenty of meat and other foods rich in Castle's extrinsic factor. As it is not unusual for pernicious anemia patients to maintain remissions for 6 months or longer without any specific therapy, it would certainly appear that weekly injections of Congo red completely fail to increase their chances of maintaining a remission. The criticism may be raised that these patients were not given sufficient Congo red and that larger or more frequent injections might have succeeded where the selected dosage failed. This is a valid objection, and it would not be safe to conclude from this experiment alone that Congo red is ineffective in pernicious anemia. The conclusion is justified, however, that weekly injections of Congo red did not furnish a practical substitute for liver extract in this group of patients, all of whom could be maintained in a complete remission by a single injection of liver extract once every 2 to 3 weeks.

TABLE 1.—BLOOD CHANGES DURING CONGO RED THERAPY.

Case No.	Patient.	Duration of R (wks.).	Total Congo red (cc.).	R. B. C. (millions).		Hb (%).		M.C.V. (μ^3).		C.I.	
				Before.	After.	Before.	After.	Before.	After.	Before.	After.
1	C. T.	9	160	4.09	2.90	90	77	95	104	1.10	1.32
2	C. M.	15	260	4.36	2.72	104	78	103	115	1.19	1.44
3	J. B.	18	360	4.36	2.66	105	74	104	112	1.20	1.39
4	I. F.	24	480	4.47	3.17	95	87	93	116	1.06	1.37
5	F. A.	25	500	4.97	1.99	101	63	92	132	1.02	1.58
6	M. A.	25	500	4.01	3.94	88	93	102	107	1.10	1.18
	Aver.	19.3	377	4.38	2.90	97	79	98	114	1.11	1.38
	Change			−1.48		−18		+16		+0.27	

More recently the opportunity arose to study the effect of Congo red in 2 cases of pernicious anemia in relapse. These patients were admitted to the ward and placed upon a diet low in Castle's extrinsic factor for some time before Congo red therapy was instituted.

This procedure eliminated any possibility of a dietary effect and at the same time established a reticulocyte baseline. In the first patient (Case 7, Chart VII), daily intravenous injections of Congo red over a 2-week period failed to produce either subjective improvement or an increase in the reticulocytes, yet a subsequent small dose of liver extract gave rise to a satisfactory reticulocyte response at the expected time with the associated subjective improvement. The second patient (Case 3, Chart III), 1 of the cases which had relapsed while receiving weekly injections of Congo red, was admitted to the ward in order to see whether intensive Congo red therapy would succeed where weekly injections had failed. This patient, given daily injections of Congo red over a 3-week period, showed a minimal reticulocyte rise to 4% on the ninth day. Since there was no subjective improvement or change in the blood levels during the 3-week period this slight reticulocytosis was most likely a non-specific response. Thus in 2 cases of pernicious anemia in relapse, daily intravenous injections of Congo red completely failed to produce clinical or hematologic improvement.

Two cases of sprue were treated with Congo red in order to determine whether the dye might exert a therapeutic effect in this disease so similar to pernicious anemia in its response to liver extract. The first patient (Case 8) had been maintained free of symptoms over a long period on a sprue diet supplemented with a single injection of liver extract every 2 to 3 weeks. The diet was kept constant and weekly injections of 20 cc. of the Congo red solution were substituted for the liver extract régime. Within 4 weeks of the last liver extract injection the patient developed nausea and diarrhea, which became so severe that after 6 weeks the dye was discontinued and liver-extract therapy renewed with almost immediate alleviation of symptoms. The second patient (Case 9) was a known sprue patient suffering from diarrhea as a result of lapsing liver extract treatment for several weeks. This patient was brought into the hospital; in spite of daily injections of 20 cc. of the Congo red solution for 1 week, the diarrhea persisted and an aphthous stomatitis developed. Both the diarrhea and the stomatitis cleared up rapidly when liver extract injections were resumed.

Case Reports. CASE 1.—C. T., female aged 42 (Chart I). Onset of fatigue, yellow pallor, and sore tongue in 1929. Remission on liver extract shortly after onset. Relapsed when liver was discontinued. First came to clinic May, 1933.

Physical Examination. Lemon-yellow pallor. Marginal papillary atrophy of tongue. Palpable spleen. *Blood:* R.B.C. 1,800,000; Hgb. 43%; C.I. 1.19. *Gastric Analysis:* No free HCl, even after histamine. *Course:* Patient was treated with intravenous liver extract at first; later 10 cc. intramuscular liver extract every 2 weeks. Blood levels rose to normal and remained there. On September 30, 1935, R.B.C. 4,090,000; Hgb. 90%; M.C.V. 95; C.I. 1.10. On this date therapy changed to 20 cc. of Congo red solution once a week. At the end of 9 weeks R.B.C. had dropped

to 2,900,000 and Hgb. to 77%; patient weak and tired, tongue very sore. Congo red discontinued and liver extract resumed with rapid symptomatic and hematologic improvement.

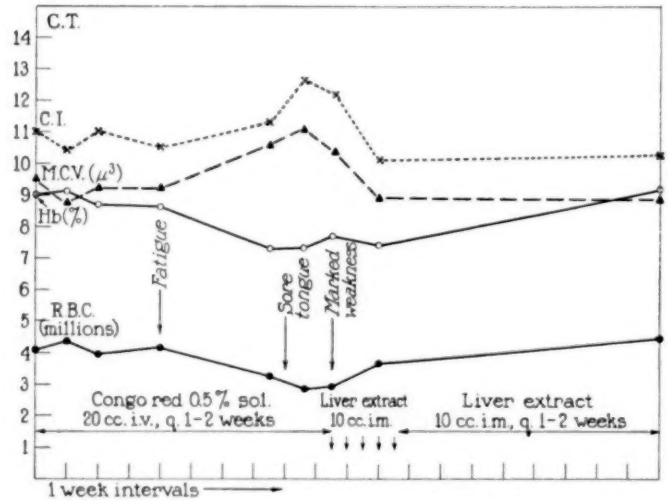

CHART I.—Case 1. Pernicious anemia. Rapid relapse during 9-week period of Congo red therapy.

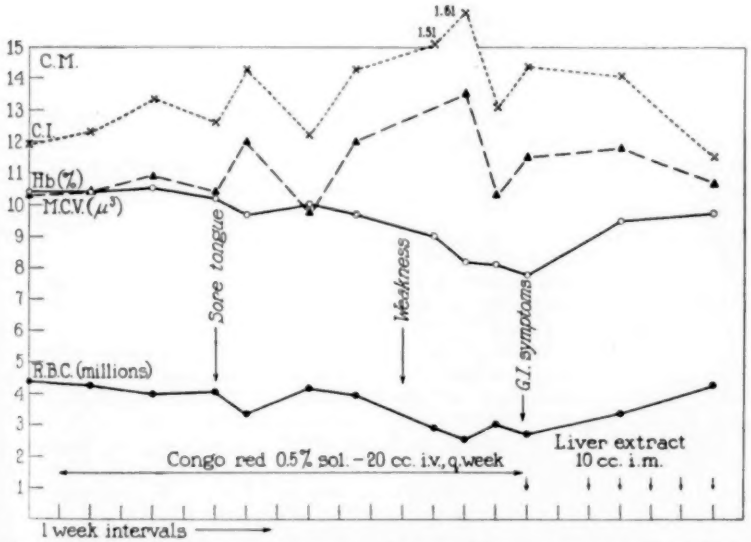

CHART II.—Case 2. Pernicious anemia. Relapse during 15-week period of Congo red therapy.

CASE 2.—C. M., male aged 60 (Chart II). In 1929 onset of fatigue, anorexia, sore tongue, paresthesias in legs, and anemia. Temporary

improvement on oral liver; incomplete response to small doses of parenteral liver extract. February, 1933, admission to the hospital. *Physical examination:* Lemon-yellow pallor, marked papillary atrophy of tongue. Palpable spleen. Slightly diminished vibratory sense in legs. *Blood:* R.B.C. 960,000; Hgb. 24%; C.I. 1.26; W.B.C. 2250. *Gastric analysis:* No free HCl even after histamine. *Bone marrow:* Typical of pernicious anemia. *Course:* Remission on intravenous liver extract. Maintained in good health with blood at normal levels on 10 cc. of liver extract intramuscularly every 2 weeks. On October 3, 1935, R.B.C. 4,360,000; Hgb. 104%; M.C.V. 103; C.I. 1.19. Therapy changed to 20 cc. Congo red solution intravenously once a week. Glossitis and weakness developed. After 15 weeks R.B.C. had fallen to 2,720,000 and Hgb. to 78%. Congo red discontinued and intramuscular liver extract resumed with rapid remission.

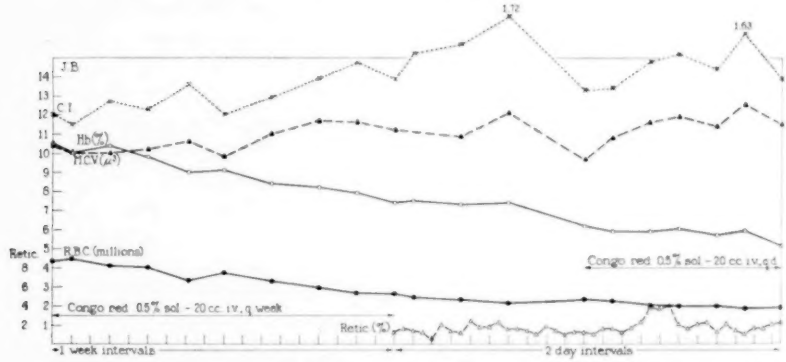

CHART III.—Case 3. Pernicious anemia. Relapse during 4-month period of weekly injections of Congo red. Failure to improve on daily injections of Congo red over 3-week period.

CASE 3.—J. B., male aged 40 (Chart III). History of onset of weakness, fatigue, anorexia, sore tongue, and yellow pallor in 1928. Diagnosis of pernicious anemia was made and patient improved on liver therapy. Treatment was irregular and he suffered several relapses. First seen at this hospital June, 1935, with R.B.C. 3,500,000 and Hgb. 94%. Liver extract 10 cc. given intramuscularly every 2 weeks; on this régime he felt very well; R.B.C. 4,360,000 and Hgb. 105%, with M.C.V. 104 and C.I. 1.20 in October, 1935, at which time therapy was changed to 20 cc. of Congo red solution intravenously once a week. This therapy was kept up for 18 weeks; during this period R.B.C. and Hgb. fell; M.C.V. and C.I. rose. He complained of increasing fatigue, exertional dyspnea, and finally soreness of tongue. He was then admitted to the hospital and placed on a meat-free diet. *Physical examination:* Moderate pallor. Redness of tongue. Slight diminution of vibratory sense in feet. *Blood:* R.B.C. 2,660,000; Hgb. 74%; M.C.V. 112; C.I. 1.39; Icteric Index 8; W.B.C. 6650. *Gastric analysis:* No free HCl even after histamine. *Course:* After 3 weeks on meat-free diet R.B.C. 2,000,000 and Hgb. 60%; icteric index 15. Daily intravenous injections of 20 cc. of Congo red solution were then given for 3 weeks. On 9th day reticulocytes had reached a low peak of 4% and then fell to original level below 2%. There was a slight fall in R.B.C. and Hgb. during the 3-week period and serum bilirubin remained elevated; the patient experienced no subjective improvement. Intramuscular liver extract therapy was subsequently renewed and blood levels rapidly returned to normal.

CASE 4.—I. F., female aged 39 (Chart IV). In 1934 onset of weakness, dizziness, pallor, anorexia, loss of weight. R.B.C. down to 1,000,000. Remission on liver extract but relapse with sore tongue and paresthesias when therapy was discontinued. Admission to the hospital July, 1935. *Physical examination:* Pallor. Slight icterus. Moderate papillary atrophy. Spleen just palpable. No neurologic disturbance. *Blood:* R.B.C. 2,080,000; Hgb. 58%; M.C.V. 121; C.I. 1.45; W.B.C. 5600. *Course:* Blood levels rose to normal on intramuscular liver extract and remission was maintained with a single injection of 10 cc. liver extract every 2 weeks. In September, 1935, R.B.C. 4,470,000; Hgb. 95%; M.C.V. 93; C.I. 1.06. Therapy changed to 20 cc. of Congo red solution once a week. After 24 weeks R.B.C. 3,170,000 and Hgb. 87%; the patient complained of weakness and sore tongue. Liver extract resumed with rapid improvement and 6 months later she is quite well with normal blood levels on a single injection of liver extract every 2 weeks.

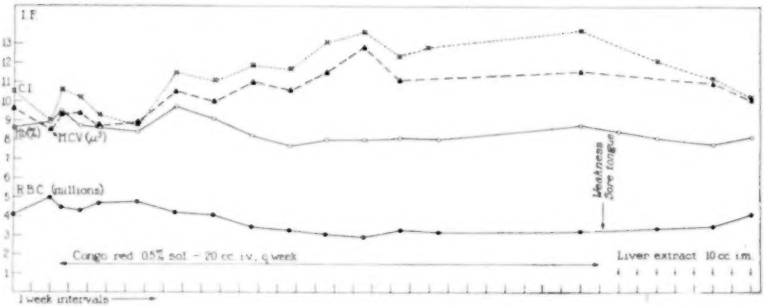

CHART IV.—Case 4. Pernicious anemia. Gradual relapse during 5½-month period of Congo red therapy.

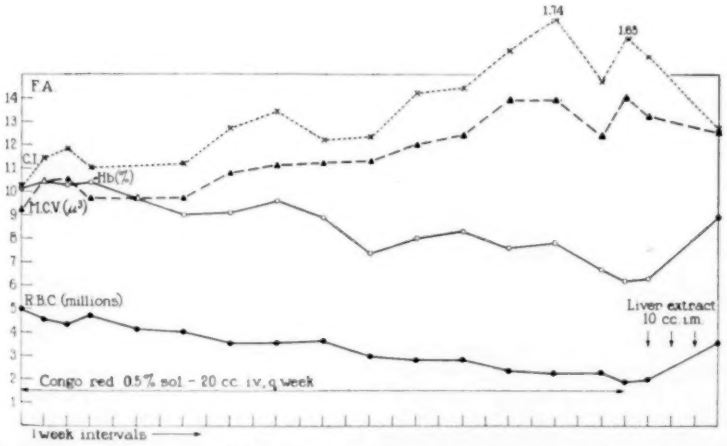

CHART V.—Case 5. Pernicious anemia. Gradual relapse during 6-month period of Congo red therapy.

CASE 5.—F. A., male aged 59 (Chart V). Onset of weakness, sore tongue, and yellow pallor in 1929. Hgb. was 35%. On oral liver extract marked

symptomatic improvement and Hgb. rose to 95%. Five years later, relapse because of inadequate therapy. April, 1935, admission to the hospital. *Physical examination:* Emaciation. Lemon-yellow pallor. Marginal papillary atrophy of tongue. Neurologic examination normal. *Blood:* R.B.C. 1,220,000; Hgb. 33%; C.I. 1.32; W.B.C. 3150; plasma bilirubin 2.65 mg.%; *Gastric analysis:* No free HCl even after histamine. *Course:* Reticulocyte peak of 25%, 5 days after intramuscular liver extract; R.B.C. and Hgb. returned to normal and patient was maintained in good health on 10 cc. of liver extract intramuscularly every 2 weeks. On September 23, 1935, R.B.C. 4,970,000; Hgb. 101%; M.C.V. 92; C.I. 1.02. Therapy changed to 20 cc. of Congo red solution once a week. At the end of 25 weeks R.B.C. 1,990,000 and Hgb. 63% with M.C.V. 132 and C.I. 1.58; moderate weakness his only complaint. Intramuscular liver-extract therapy resumed with rapid return of blood levels to normal.

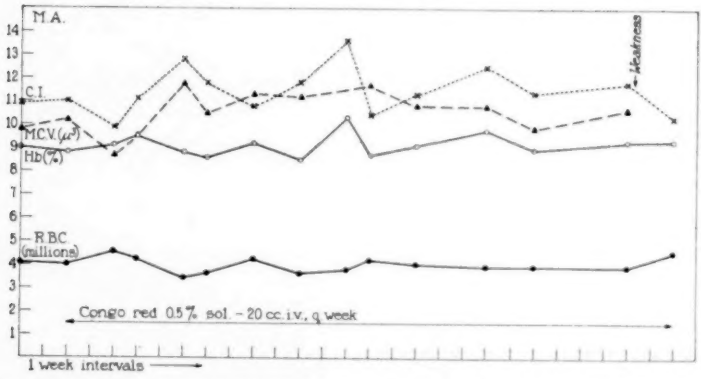

CHART VI.—Case 6. Pernicious anemia. Course of blood count during 6-month period of Congo red therapy. In contrast with Cases 1 to 5 this patient showed no essential change in blood picture.

CASE 6.—M. A., female aged 37 (Chart VI). Three-year history of weakness, pallor, sore tongue and anemia. Temporary remission on liver extract. Discontinued therapy and admitted in relapse in February, 1935. *Physical examination:* Lemon-yellow pallor. Extreme papillary atrophy of tongue. Palpable spleen. Sluggish tendon reflexes. *Blood:* R.B.C. 1,115,000; Hgb. 35%; M.C.V. 134; C.I. 1.51; W.B.C. 3500. *Course:* Reticulocytes rose to 21% following intramuscular liver extract; R.B.C. and Hgb. returned to normal. Complete remission maintained with 10 cc. liver extract intramuscularly every 2 weeks. On October 10, 1936, R.B.C. 4,010,000; Hgb. 88%; M.C.V. 102; and C.I. 1.10. Therapy changed to 20 cc. Congo red solution intravenously once a week. After 25 weeks, no definite symptoms of relapse and no appreciable change in blood levels. Therapy changed back to liver extract.

CASE 7.—F. G., Italian male aged 54 (Chart VII). Admitted to hospital September 3, 1935. History of weakness, loss of weight, and dizziness for 2½ years. Temporary improvement on oral liver. Symptoms recurred when he stopped liver therapy. Developed anorexia, abdominal discomfort, and paresthesias in extremities. *Physical examination:* Moderate pallor. Marginal papillary atrophy of tongue. Slight diminution of vibratory sense in feet. *Blood:* R.B.C. 2,490,000; Hgb. 76%; M.C.V. 133; C.I. 1.52; W.B.C. 4400. *Gastric analysis:* No free HCl, even after histamine.

Course: Patient was placed upon meat-free diet for several weeks; weakness and indigestion increased; tongue became sore. Reticulocytes stabilized below 2%. Congo red solution (20 cc.) given daily for 6 days, followed by 40 cc. daily for 5 days. No rise in reticulocytes in 2 weeks. Patient then given single injection of 5 cc. liver extract (the amount derived from 25 gm. of whole liver) intramuscularly. Reticulocytes reached peak of 9% on 6th day with marked subjective improvement. Complete blood remission followed further liver-extract therapy, and for the past year the patient has remained symptom-free with normal blood levels on 10 cc. of liver extract intramuscularly every 2 weeks.

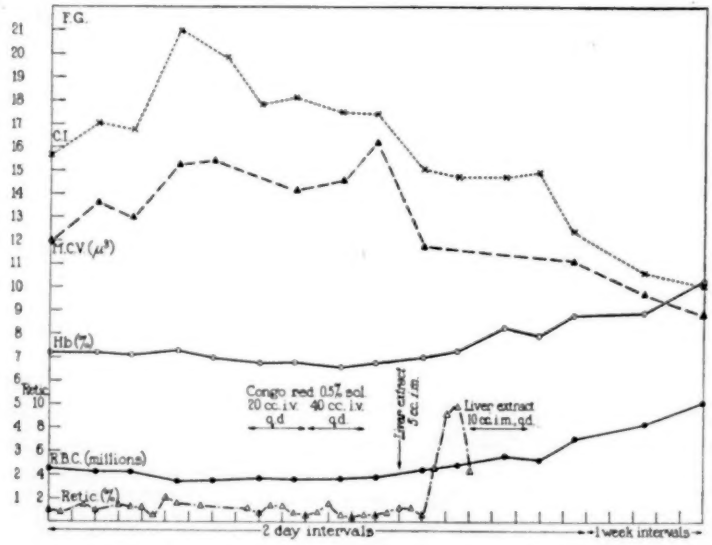

CHART VII.—Case 7. Pernicious anemia in relapse. Failure of daily injections of Congo red to modify the blood picture. Subsequent response to liver extract.

CASE 8.—R. D., female aged 50, had lived in China 21 years. During the last 7 years of her stay she suffered from repeated attacks of diarrhea associated with soreness of tongue and mouth. Temporary relief of symptoms on diet of liver and sour milk. Later recurrence; oral liver extract failed to give relief. Severe anemia developed. Patient admitted to the hospital in 1931. *Physical examination:* Marked emaciation and pallor. Papillary atrophy of tongue. Palpable spleen. *Blood:* R.B.C. 820,000; Hgb. 22%; M.C.V. 131; C.I. 1.34; icteric index 20. *Gastric analysis:* Free HCl present only after histamine injection. *Course:* With intensive parenteral liver-extract therapy, diarrhea ceased, soreness of tongue cleared, and blood levels returned to normal. For the next 4 years she remained symptom-free on sprue diet augmented by an intramuscular injection of 10 cc. of liver extract every 2 to 3 weeks. If she tried to increase the interval between liver-extract injections to 4 weeks or longer, she invariably developed gastro-intestinal symptoms which were in turn rapidly alleviated by a single injection of liver extract. In December, 1935, therapy was changed from an intramuscular injection of liver extract once every 3 weeks to weekly intravenous injections of 20 cc. of Congo red solution. The diet

was kept constant. Within 4 weeks of the last liver extract injection nausea and diarrhea set in. These symptoms increased in severity; at the end of 6 weeks the Congo red injections were abandoned and an injection of 10 cc. of liver extract was given intramuscularly. Within 36 hours of this liver extract injection, all symptoms had vanished.

CASE 9.—B.M., female aged 37, had resided for 12 years in Cuba. For 7 years recurrent attacks of diarrhea, nausea, vomiting, and abdominal cramps. Two years after onset of diarrhea sore mouth and anemia developed. Temporary improvement on sprue diet and oral liver extract; later symptoms recurred and failed to respond to oral therapy. Admission to hospital February, 1935. *Physical examination:* Marked pallor. Papillary atrophy of tongue with aphthous ulceration of buccal mucosa. Abdominal distention. *Blood:* R.B.C. 2,000,000; Hgb. 66%; M.C.V. 135; C.I. 1.65. *Gastric analysis:* Free HCl present after alcohol test meal. *Course:* On intramuscular and intravenous liver extract symptoms ceased and blood levels returned to normal. After discharge from the hospital patient was symptom-free for nearly a year on a sprue diet with a single intramuscular injection of 10 cc. of liver extract every 2 weeks. She then lapsed treatment and soon developed severe diarrhea and soreness of the tongue. She was readmitted to the hospital and given daily intravenous injections of 20 cc. of Congo red solution for 1 week. During this period diarrhea continued and a crop of aphthous ulcers appeared in the mouth. She was then given daily intramuscular injections of liver extract for 5 days. Soreness of the tongue disappeared after the first injection and the aphthous ulcers healed rapidly. Diarrhea ceased after the third injection of liver extract. The patient has since been maintained in excellent health on injections of liver extract once or twice a week.

Comment. There is obviously a marked discrepancy between the results that we obtained with Congo red and those reported by Massa and Zolezzi. Recently Lendvai,[4] in Budapest, has published a series of 12 cases of pernicious anemia treated with intravenous Congo red. All of his patients were in severe relapse with erythrocyte counts varying from 800,000 to 2,200,000 red blood cells per c.mm. and hemoglobin levels of 28 to 64%. They received from 8 to 20 injections of 10 cc. of a 0.5% solution of Congo red over periods of 10 days to 4 weeks. Reticulocytes were followed in all cases and 4 cases showed slight reticulocyte rises of 4 to 8%; there was no increase in the reticulocytes in the other 6 cases. In no case did the red blood cell count or the hemoglobin rise above the pretreatment levels. Subsequent treatment with liver effected a complete blood remission in every case. Bone marrow was aspirated at intervals during the period of observation; the smears from the marrow presented a megaloblastic picture before and after Congo red therapy but a normoblastic picture after liver-extract therapy. Lendvai regards the slight reticulocytosis noted in certain of his cases as non-specific in type and concludes that Congo red exerts no therapeutic effect in pernicious anemia. The results of Lendvai are wholly in accord with those that we obtained in the treatment of pernicious anemia with Congo red.

Since the 2 cases of Mermod and Dock were changed to liver therapy as soon as reticulocyte rises had been produced with Congo

red, there is no evidence that these reticulocyte crises differed in any way from the non-specific responses noted by Lendvai. Certainly there is no justification for assuming a specific therapeutic effect of Congo red in these 2 cases.

Thus the contention of Massa and Zolezzi that Congo red may bring about a complete blood remission in pernicious anemia lacks definite confirmation to date. It is quite impossible to reconcile the results reported by the Italian authors with our observations or those of Lendvai. One can only suggest: 1, that the Italian cases did not have true pernicious anemia, or 2, that they may have been individuals with "incomplete pernicious anemia." Goldhamer,[3] has demonstrated the presence of a small amount of intrinsic factor in the gastric juice of patients with pernicious anemia. It is conceivable that the gastric secretion of Massa and Zolezzi's responding cases contained a fair amount of intrinsic factor; that these patients had had diets poor in extrinsic factor prior to their admission to the hospital; and that they had received far better diets in the hospital. If such were the case, they might then have been able to manufacture through the combination of extrinsic and intrinsic factors in their gastro-intestinal tracts sufficient "liver extract" to bring about blood remissions. In other words, the remissions may have been dietary in origin and not due to the Congo red.

Finally, let us assume for the moment on the basis of Massa and Zolezzi's observations that Congo red might exert some therapeutic effect in pernicious anemia. Even so, Congo red could not be compared with the active principle of liver extract, for Dakin and West[2] have shown that 80 mg. of their purified fraction is sufficient to bring about a maximal reticulocyte response and an increase in the blood levels of patients with pernicious anemia. If Congo red even approached this active principle in potency, then our 2 cases in relapse and the 10 cases of Lendvai, which received 400 to 2100 mg. of the dye over relatively short periods, should certainly have shown striking improvement in both the clinical and the hematologic picture.

Conclusion. Congo red is totally ineffective in the treatment of patients with pernicious anemia or sprue. The dye may occasionally produce slight non-specific reticulocyte rises in cases of pernicious anemia.

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EFFECT OF LEAD THERAPY ON BLOOD CELLS OF CANCER PATIENTS.

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Since the stimulating researches of Blair Bell on the use of lead compounds in the treatment of cancer, much experimental work has been done and varying opinions are still held regarding the efficacy of this agent. Because recently Bargen, *et al.*,[2] of the Mayo Clinic, reported some encouraging results with the use of lead in inoperable cancer, a similar study was undertaken at this hospital. This paper deals with the blood changes resulting from the use of colloidal lead in a group of 22 cases of advanced cancer.

Method. Colloidal lead triphosphate was prepared in this laboratory and given to patients with late cancer, according to the procedure outlined by Bargen. It was administered intravenously 2 or 3 times weekly, in doses varying from 35 to 140 mg. (10 to 40 cc.) over a period of 2 to 4 weeks. Five cases received an incomplete course of treatment, totaling 175 to 280 mg. and 17 cases were given a full course of treatment totaling 535 to 805 mg. A complete blood count, including hemoglobin (Haden-Hausser), total erythrocytes, stippled erythrocytes, total white blood cells and differential, was made before treatment, 2 to 4 times weekly during treatment, twice weekly for 4 weeks following treatment and once monthly thereafter. In 18 cases the count of stippled red blood cells as obtained by the Wright's stain was checked with Manson's borax methylene blue stain. In 1 (Case 22), stippled erythrocyte counts with Wright's stain, basophilic aggregation counts with Manson's stain, and reticulocyte counts with cresyl blue were made 2 to 4 times weekly for 9 weeks.

Effect of Lead on the Red Blood Cells. A. *Findings of Previous Workers.* 1. The *anemia* of lead poisoning results from the destruction of the "leaded" cells in the peripheral circulation.[1a,15] In rabbits, after the ingestion of 1 gm. of lead, the number of circulating red cells may decrease more than 20%.[12b] In some cancer patients reductions of approximately a million cells may occur within an hour after a single injection of lead.[3b] Along with the destruction of circulating erythrocytes there is a compensatory regeneration. Early in lead intoxication a large number of nucleated and of reticulated red blood cells appear in the peripheral circulation.[1a,12a] Aub[1b] reported 6 to 16% reticulocytes in total red blood cell counts of 3,500,000.

2. *Irregularities in size*[8] and *shape*[6] of the red cells occur.

3. *Nucleated Red Blood Cells.* In shipbreakers exposed to a heavily leaded atmosphere Ferguson and Ferguson[8a] found nucleated red cells in 56% of the blood films examined and in at least one film from every case. Of the nucleated cells 99% were normoblasts and 1% were megaloblasts. Bell, Williams and Cunningham[4] repeatedly observed nucleated red cells as early as the fifth day following intravenous injection of lead. In Bell's work with lead therapy in cancer, nucleated red corpuscles were frequently found, and when present were invariably associated with considerable anemia and with stippling of red cells. Occasionally the nucleated red cells contained basophilic granules in their cytoplasm.

4. *Reticulocytes.* Fleckel and Tschernow[9] approximated the degree of lead absorption in patients by determining the percentage of reticulocytes by vital staining. They regarded 0.7 to 1% reticulocytes as normal. Jones[11] (1933) and McCord and his coworkers[13] (1934) advocated the use of the reticulocyte count as an index of lead absorption in place of the usual punctate basophilia count. Brookfield, and later the Fergusons, found a close correlation between the number of reticulocytes and the number of cells showing punctate basophilia.

5. *Polychromasia.* Polychromasia is always present in the immature erythrocytes of the normal bone marrow. In the peripheral blood, polychromasia is seen in the nucleated red cells and occasionally in immature non-nucleated reds, especially in anemias that are associated with active erythrocyte production. Bell's group of investigators[3c] believed that polychromasia is a regenerative phenomenon observed constantly in lead anemia in association with punctate basophilia.

6. *Stippling.* Punctate basophilia or stippling of red blood corpuscles has long been recognized as one of the earliest and most constant phenomena in lead poisoning. Pappenheim,[14] Schilling-Torgau,[8b] Key[12a] and Brookfield[6] believe that polychromasia, stippling and reticulation are all due to the presence of basic staining cytoplasm of youthful origin, and are all substantially the same substance. Punctate basophilia is present classically where bone marrow is excessively active; it is regarded by some[1,4,6,8a,10] as a degenerative phenomenon occurring in young red blood cells. It never occurs in aplastic anemia,[8a] in which condition there is a suppression of erythrocyte formation, but it does occur chiefly in toxic anemias where the products of red-cell degeneration are retained within the body. Ferguson and Ferguson found stippling present in every slide examined during the course of their lead investigation in shipbreakers. Of the nucleated red cells seen on their slides 4% showed basophilic stippling, whereas only 0.9% of all erythrocytes showed the punctate basophilia.

B. *Findings in Present Study.* 1. A progressive *anemia* was noted after the completion of treatment in 16 of our 22 cases (Tables 1, 2). A decrease of 20% in hemoglobin and erythrocytes during or following treatment was regarded as significant, and in most cases (11 of the 16 which developed anemia) was noted 1 to 3 weeks

TABLE 1.—EFFECT OF LEAD ON HEMOGLOBIN AND ERYTHROCYTES. (ALL CASES EXCEPT 8 AND 22 DIED WITHIN A FEW DAYS AFTER THE LAST COUNT WAS TAKEN.)

		Before treatment.			After treatment (last count taken).			
Case.	Lead (mg.)	Hb. (gm.)	R. B. C. (millions)	C. I.	Hb. (gm.).	R. B. C. (millions)	C. I.	Weeks after treatment.
1	770	14.4	4.67	0.92	6.5	2.74	0.71	18
2	805	11.5	3.36	1.02	6.5	2.84	0.72	5½
3	805	10.0	3.76	0.80	5.5	3.21	0.51	9
4	805	12.5	4.40	0.92	6.0	2.27	0.79	22
5	805	8.0	4.12	0.58	5.5	2.88	0.57	11
6	805	10.5	3.37	0.93	9.0	3.04	0.89	18
7	805	11.0	3.51	0.94	8.5	3.24	0.78	5
8	805	12.0	3.86	0.93	12.5	4.05	0.93	33; still living after 48 weeks.
9	805	12.0	4.01	0.89	11.0	3.98	0.82	2
10	630	11.0	3.61	0.91	10.0	3.70	0.81	0
11	805	13.0	4.25	0.91	7.0	2.55	0.82	9
12	280	12.5	4.15	0.90	10.0	3.66	0.81	5
13	805	11.0	3.67	0.90	9.3	3.22	0.85	4
14	805	12.0	4.02	0.89	8.0	3.05	0.78	25
15	210	10.5	3.64	0.86	7.5	3.14	0.72	3
16	805	11.0	3.62	0.91	6.0	2.88	0.62	3
17	535	10.0	3.86	0.79	9.3	3.36	0.82	1
18	642	11.0	3.10	1.06	9.2	3.55	0.77	2
19	175	9.0	2.99	0.90	9.0	2.65	1.00	4
20	280	10.5	3.69	0.85	5.0	2.45	0.61	13
21	175	8.5	3.34	0.76	5.5	2.61	0.63	7½
22	595	13.5	4.51	0.89	9.5	3.40	0.83	7; still living after 21 weeks.

TABLE 2.—SHOWING DEVELOPMENT OF ANEMIA AFTER LEAD TREATMENT IN A TYPICAL CASE (CASE 11).

Date, 1936.	Lead (mg.).	Hb. gm.	R. B. C. (millions)	Date, 1936.	Hb. gm.	R. B. C. (millions)
Jan. 31		13.0	4.25	Feb. 20	10.5	3.65
Feb. 3	35			Feb. 24	9.5	3.11
Feb. 4	...	12.5	4.27	Feb. 28	10.0	3.23
Feb. 5	70			Mar. 2	8.5	3.20
Feb. 6	...	11.5	3.90	Mar. 9	8.0	3.54
Feb. 7	105			Mar. 13	9.0	3.22
Feb. 8	...	12.0	3.83	Mar. 16	9.0	3.39
Feb. 10	140			Mar. 20	8.0	2.79
Feb. 11	...	11.5	3.89	Mar. 25	8.5	2.70
Feb. 12	140			Apr. 1	7.5	2.84
Feb. 13	...	11.0	3.50	Apr. 8	7.5	2.60
Feb. 14	140			Apr. 15	6.7	2.87
Feb. 15	...	10.5	3.59	Apr. 22	7.0	2.55
Feb. 17	140			Apr. 24 Expired		
Feb. 18	...	10.5	3.36			
Feb. 19	35					
Total	805					

after the last dose of lead. In 3 cases such a significant decrease was not found until after 7 or 8 weeks. One patient developed anemia during the course of treatment and one showed an anemia 1 day after the last dose of lead. These 16 cases showed a pronounced drop in color index, which is attributed to the destruction of mature erythrocytes relatively rich in hemoglobin and their partial replacement by immature erythrocytes relatively deficient in hemoglobin. The immature cells include reticulocytes, polychromatic cells, stippled cells and nucleated red cells. With the exception of Case 5, there were significant decreases in the color index ranging from 0.04 to 0.30, with an average drop of 0.15 in color index during the interval from the first to the last count taken. Of the 6 cases which did not develop a significant anemia, 4 (Cases 9, 10, 17, 18) died within 2 weeks after treatment, 1 (Case 19) died 4 weeks after receiving only 175 mg. of lead, and 1 (Case 8) is still alive having developed no anemia following a full course of 805 mg. of lead.

2. *Anisocytosis and poikilocytosis* of varying degree were noted in practically all the films studied.

3. *Nucleated red blood cells* were found in the smears in 20 of the 22 cases studied. Of these 20 cases all showed normoblasts and 6 (30%) also showed megaloblasts. Of the total number of nucleated cells counted, 4% were megaloblasts. Normoblasts were noted as early as 8 days after the completion of treatment and as late as 4 months, the average time of their appearance being about 3 weeks. Two cases (Cases 10, 15) at no time showed nucleated red cells in their blood smears. One of these (Case 10) received 630 mg. of lead and died 2 weeks after the onset of treatment, while the other (Case 15) received but 210 mg. of lead and died 4 weeks after the initial treatment.

4. *Reticulocyte counts* were made in one typical case (Case 22, Table 3). It was found that the percentage of reticulocytes closely paralleled, and was somewhat higher than, the percentage of stippled cells on every occasion when the two counts were checked. In some cases reticulocyte counts of over 5% were found.

5. *Polychromasia* and achromasia were noted in most of the slides.

6. *The stippled cell* counts were made from smears treated with Wright's stain. In 18 cases this count was checked with the basophilic aggregate count in smears stained by Manson's borax—methylene blue method. A stippled cell count of 1% or over, which was taken as significant of plumbism, was found in 17 of our 22 cases, and was reached in from 1 to 8 weeks (average $3\frac{1}{2}$ weeks) after the start of treatment. The highest stippled cell count found was 15% (Case 11). Over 50% of nucleated cells showed basophilic stippling of their cytoplasm.

7. *The basophilic aggregation* stains were not satisfactory. There was difficulty in preventing precipitation of the methylene blue stain, particularly in warm weather. According to McCord *et al.*,

the basophilic aggregation stain reveals all the basophilic substance of the erythrocytes including the polychromatophilia, reticulation and the punctate stippling. Our tabulations show that the basophilic aggregation count instead of being higher than the stippled red count, was lower in most cases. In Case 22 the reticulocyte count was higher than the basophilic aggregation count on each of the 19 dates when the two counts were checked (Table 3).

TABLE 3.—COMPARISON OF PERCENTAGES OF STIPPLED CELLS, BASOPHILIC AGGREGATES, AND RETICULOCYTES (CASE 22).

Date, 1936.	Stippled cells (Wright's stain).	Basophilic aggregates (Manson's stain).	Reticulocytes (cresyl-violet stain).
July 21	1.2	0.77	1.4
July 24	1.5	0.73	2.2
July 27	1.0	0.88	2.2
July 28	1.2	0.77	2.2
July 31	1.4	1.10	1.8
Aug. 3	1.2	0.80	2.0
Aug. 5	1.2	0.91	2.2
Aug. 6	1.4	1.00	2.2
Aug. 8	0.8	0.71	1.6
Aug. 10	0.8	0.82	1.2
Aug. 11	1.8	0.75	1.8
Aug. 13	1.8	0.64	2.2
Aug. 22	1.2	1.10	1.4
Aug. 27	1.4	0.70	2.2
Aug. 31	4.4	3.20	5.0
Sept. 4	4.2	3.30	5.0
Sept. 9	5.6	3.30	5.4
Sept. 11	4.4	3.20	5.0
Sept. 14	5.6	4.80	5.8

8. *Cabot ring cells* were found 10 times in 6 cases. *Howell-Jolly bodies* were found twice.

Effect of Lead on the White Blood Cells. A. *Findings of Previous Workers.* The literature contains relatively few reports on the effect of lead intoxication upon the white cells and these reports are conflicting. In animal studies, McLean[16] found an immediate neutrophilic leukocytosis which was followed in about 8 hours by an increase in lymphocytes and monocytes; Aub *et al.* found a lymphocytosis, while Ophüls[16] found myelocytes in the peripheral circulation. In clinical cases, little effect on the leukocytes was noted according to Pepper and Farley.[16] Biondi[5] reported eosinophilia and mononucleosis but considered them as of only slight relative importance in plumbism. Bell *et al.*[4] found that in patients with cancer a slight leukocytosis followed moderate doses of lead, and a marked leukocytosis resulted from large doses. The earlier the count was made after the injection the greater the likelihood of finding a leukocytosis. A relative lymphocytosis occasionally occurred and a slight eosinophilia appeared to be fairly common. Brookfield reported that in cancer patients with lead intoxication the only constant change was a tendency for an "increase" in monocytes of from 3 to 5%. Ferguson and Ferguson reported a

general shift of neutrophils to the right, in their cases of chronic plumbism among shipbreakers. Cadwalader[7] reported myelocytes in the peripheral blood stream of a patient with lead intoxication.

B. *Findings in Present Study.* 1. *Leukocytosis* was noted in 14 cases (Table 4), in which it occurred 1 to 12 weeks (average 6½ weeks) after the beginning of treatment, or from 1 day to 8 weeks (average 3½ weeks) after the last treatment.

TABLE 4.—EFFECT OF LEAD ON WHITE BLOOD CELLS. NOTE THAT FIRST 14 CASES ONLY SHOW MARKED LEUKOCYTOSIS.

Case.	Lead mg.	Before treatment.						After treatment.						Weeks after treatment.
		Total.	Neut.	Ly.	Mon.	Eos.	Bas.	Total.	Neut.	Ly.	Mon.	Eos.	Bas.	
1	805	11,900	58	33	6	1	..	21,600	66	31	3	..	..	18
2	805	10,750	48	36	13	2	1	14,200	76	22	2	..	..	9
3	805	8,950	79	9	7	4	..	43,750	91	3	6	..	..	9
5	805	7,350	69	21	4	5	..	17,650	98	1	1	..	..	15
6	805	6,750	72	14	9	5	..	10,500	88	5	6	1	..	16
7	805	6,000	75	8	8	8	..	13,050	90	5	5	..	..	5
10	630	14,300	79	13	6	1	1	26,750	96	3	1	..	..	1 day
12	280	9,600	64	25	10	..	1	18,650	95	2	3	..	..	4
13	805	8,100	62	29	5	3	1	16,400	85	6	9	..	..	4
15	210	6,300	69	14	9	6	2	17,350	85	8	7	..	..	4
16	805	11,150	79	13	7	1	..	20,100	95	2	3	..	..	1½
18	642	8,500	83	10	3	4	..	24,550	92	3	5	..	..	2
19	175	3,100	70	14	8	8	..	8,550	91	2	7	..	..	4
21	175	12,700	78	12	7	3	..	21,350	81	6	13	..	..	7
4	805	4,700	63	28	6	2	1	6,150	93	3	4	..	..	22
8	805	8,000	64	33	3	..	..	6,750	51	39	5	4	1	35
9	805	8,950	71	28	1	..	..	10,150	70	19	7	4	..	2
11	805	10,950	63	31	6	..	..	12,950	81	14	5	..	..	8½
14	805	10,400	37	50	9	4	..	7,700	60	36	1	2	1	28
16	805	11,150	79	13	7	1	..	12,400	88	6	6	..	..	4
17	535	23,550	81	10	7	2	..	18,100	94	2	1	3	..	1
22	595	9,700	76	20	4	..	..	5,550	64	30	5	1	..	..

2. *Differential Count.* The leukocytosis was associated with an absolute increase in number of neutrophils which rose to as high as 98% of the total white cell count. The lymphocytes were relatively and absolutely decreased in number to as low as 1% of the total white count. In no case was a lymphocytosis noted. Eosinophil and basophil counts were normal throughout. In one instance a slight monocytosis of 11% was noted.

3. *Basophilic Granulation of Neutrophils.* In all of our cases, after the beginning of treatment, there appeared an increase in basophilic granulations in the cytoplasm of the neutrophils. In some (Cases 6, 18, 19, 20) most or all of the neutrophils counted showed this granulation.

4. In 9 of our cases, *myelocytes* were noted in the peripheral blood. In 4 of these 9 the myelocytes made their appearance within 2 weeks after the beginning of treatment.

Summary. 1. Among 22 patients with advanced cancer, treated with colloidal lead triphosphate, a progressive anemia developed in most cases several weeks after the treatment had been completed. None of the cases showed a substantial improvement in the blood condition after cessation of treatment.

2. Nucleated red cells appeared in the peripheral circulation

almost simultaneously with the development of a moderate anemia, both appearing on the average about 3 weeks after the completion of treatment. Over 30% of the cases showing normoblasts also showed megaloblasts. Over 50% of all the normoblasts showed basophilic stippling of their cytoplasm.

3. The reticulocyte count closely paralleled the stippled red cell count. The reticulocyte count was a good measure of the bone marrow response to the anemia of the patient.

4. The basophilic stippled cells appeared in the peripheral blood at approximately the same time as the young erythrocyte forms. Stippled counts as high as 15% were found in some smears.

5. Counting of "basophilic aggregations" with the Manson stain was found to be unreliable. In only 25% of our counts was the basophilic aggregate percentage higher than the stippled cell percentage. The reticulocyte count was higher than the basophilic aggregate count on every occasion where the two were checked.

6. Cabot ring cells and Howell-Jolly bodies were noted occasionally.

7. Leukocytosis was noted in most of our cases and was usually marked. The average time of its appearance was $3\frac{1}{2}$ weeks after the onset of treatment.

8. Basophilic ("toxic") granulation was found in the cytoplasm of the neutrophils in all cases studied.

9. In 9 cases, myelocytes were found in the peripheral blood, 2 weeks or more after the beginning of lead therapy.

10. A relative and absolute lymphopenia was found in most cases, and in no instance was a lymphocytosis noted.

11. In 1 case a slight monocytosis was found.

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ACUTE HEMOLYTIC ANEMIA (LEDERER TYPE).

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The hemolytic anemias belong to one of the most interesting but controversial and confusing chapters of clinical hematology. They include many varieties which have in common the process of intravital destruction of red blood corpuscles by excessive hemolysis. A considerable group of hemolytic anemias may be designated as "symptomatic." In these, the hemolysis is but a symptom of the underlying process which is mostly an acute intoxication by chemical poisons (lead, arsenicals, potassium, chlorate, etc.), bacterial toxins (sepsis, malaria, etc.), or certain drugs and foods. Another group represents a disease *sui generis;* the factor causing the hemolysis is here permanently present, a kind of constitutional dysfunction of the hematopoietic system. We have in this instance a constitutional damage of the produced erythrocytes thus markedly decreasing their vitality (congenital hemolytic icterus, sickle-cell anemia, etc.).

This paper will deal not with either of these groups, but with a variety recently recognized that may be considered as a well-characterized group.

Lederer,[39a] in 1925, reported 3 cases of acute hemolytic anemia "probably of infectious origin." It occurred in 2 males and 1 female, the age ranging from 16 months to 25 years. The onset was characterized by rapid development of pallor, icterus, weakness, rise of temperature and evidence of hemolysis. The blood picture was dominated by a very profound rapidly progressive anemia with marked leukocytosis and erythroblastemia. A striking feature was the dramatic response to blood transfusion with prompt cessation of hemolysis and complete recovery.

A number of reports of this type of anemia has since appeared. No doubt this is not a new disease. The case of MacIntosh and Cleland[44] (1902) of rapidly increasing anemia with irregular pyrexia and death, and the 2 cases of Morawitz[47a] (1907) of atypical grave anemia with recovery, appear to belong to this group of acute hemolytic anemias. He suggested an infectious agent as the cause of the acute destruction of the erythrocytes. Cases described under different titles, such as acute febrile, acute infectious anemia (Brill,[7] Steffens,[63] Eimer,[21] and others) and some of the reported recoveries from acute leukemia or "leukanemia" (Teeter,[65] Pearce,[59] and others) also appear to belong to this well-defined group of acute

hemolytic anemias. But due to diagnostic difficulties, this form of anemia has no doubt previously escaped recognition.

The following report is based on 3 cases of this kind of anemia.

Case Reports. Case 1.—N. A., a white female child, aged 4 years, patient of Dr. K. T. Knode, had always enjoyed good health and since birth had been under his supervision. She was seen by him 2 weeks previous to the present illness, in a periodic visit to his office, apparently in good health. The present illness was preceded by a slight upper respiratory infection of several days' duration. On February 6, 1936, the child suddenly became ill with chills, fever, some vomiting and marked pallor. The skin was

Table 1.—Blood Examination in Cases 1 and 2.

Date.	Hb., %.	Hb., gm. (photolometric).	Erythrocytes per c.mm., millions.	Color index.	Leukocytes per c.mm.	Myelocytes, %.	Neutrophils, %.	Lymphocytes, %.	Erythroblasts, %.	Reticulocytes, %.	Fragility of erythrocytes.	Bilirubin in serum (photolometer), mg. %.	Van den Bergh direct.	Urobilin in urine.	Stained smears.
Case 1. 1936.															
Feb. 9	27	4.0	1.5	0.9	42.3	6	84	10	2.2	15.0	..	1.80	Weak pos.	++++	Red cells; marked anisocytosis, macrocytosis, polychrom.
10	19	2.9	1.3	0.7	28.0	6	82	12	1.7	..	Nor.	1.95	Weak pos.	++++	
*13	36	5.4	1.6	1.2	..	3	84	12	..	25.0	..	..	..	+++	
*17	60	8.9	2.7	1.2	5.0	0	55	..	..	11.0	..	0.80	Neg.	+	Lcts., marked shift to left.
20	67	10.0	2.6	1.3	6.8	0	25	72	..	10.0	Nor.				
24	85	12.7	4.3	0.9	5.5	..	..	..	..	2.0					
28	88	13.1	4.2	0.9	7.2	0	53	45	..	2.0	..	0.40	Neg.	Neg.	Slight anisocytosis.
Apr. 15	105	15.6	5.3	0.9	7.2	0	46	52	..	0.5	..	..	..	..	No abnormalities.
June 20	108	15.8	5.4	1.0	8.0	0	58	42	..	..	..	..	..	..	No abnormalities.
Case 2. 1935.															
Nov. 16	27	4.1	1.7	0.8	45.0	10	82	8	4.2	28.0	..	2.80	Weak pos.	++++	Marked anisocytosis, many macrocytes, marked basophilic degeneration.
*18	39	5.4	2.2	0.9	31.5	6	77	13	2.2	20.0	Nor.	..	..	..	
21	43	6.4	2.3	0.9	14.9	4	79	17	1.0	9.5	..	1.50	Weak pos.	+++	
29	63	9.3	3.2	1.0	11.6	3	79	15	0.8	8.8	..	0.90	Neg.		
Dec. 3 1936.	69	10.3	3.5	1.0	8.9	0	67	25	0.1	4.5	..	0.40	Neg.		
Jan. 3	103	15.4	5.2	1.0	12.7	0	70	25	..	0.5	..	0.20	Neg.	Neg.	
Apr.	104	15.5	5.3	1.0	10.8	0	70	30	..	..	..	..	..	..	Normal.
June	105	15.8	5.3	1.0	9.8										

* After transfusion.

definitely icteric, the urine dark reddish-brown and the temperature 102° F. Physical examination was essentially negative. On February 9, she was seen in consultation by one of us (A.S.G.). She appeared very apathetic; the skin was moist, pale and icteric. The scleræ were moderately yellow tinged. The blood count revealed marked anemia and leukocytosis with hemoglobin 27%, and evidence of regeneration, macrocytosis and hemolysis (Table 1). The urine showed a strong reaction for urobilin. The van den Bergh direct reaction was faintly positive and the serum bilirubin was 1.8 mg. %. The patient appeared critically ill and on the following day she was admitted to the Epworth Hospital, at which time the skin was still slightly icteric with extreme pallor. The liver and spleen were not palpable. The temperature was 104° F., pulse rate 130, and respiration 20 per minute. The hemoglobin had fallen to 19% (2.9 gm. %), erythrocytes 1.3 millions,

leukocytes 28,000 per c.mm. (differential count unchanged). The fragility test of erythrocytes was within normal limits. The serum bilirubin was 1.95 mg. % and the van den Bergh direct reaction was faintly positive. The blood culture was negative. The urine appeared to be bile tinged, but the bile test was negative. Albumen was 3+. Urobilin increased and the microscopic examination of the urinary sediment revealed many granular casts. In view of the critical condition the child was transfused with 200 cc. of her father's citrated blood. This treatment was followed by an immediate rapid improvement and the child's general condition became distinctly brighter. The skin was warm and moist. The temperature fell to 102° F. The same day intramuscular liver extract therapy was instituted and 2 days later another 200 cc. of citrated blood were given. The child made a speedy and complete recovery and left the hospital on the fifteenth day after admission. She has since remained in good health and the blood examination done 4 months later, June 29, 1936, revealed a perfectly normal blood picture (Table 1). Liver therapy was discontinued 1 month after discharge from hospital. There was no history of anemia, jaundice, or any blood disturbance on either side of the family and no history of drug-taking could be elicited.

Case 2.—Mr. G., a white male, aged 40 years, superintendent of a factory by occupation and patient of Dr. M. Whitlock, was in good health until the present illness. The illness began about November 11, 1935, as a mild upper respiratory infection, for which he was treated by the usual medication. No improvement occurred during the next 5 days and on November 16, he suddenly became very weak with high fever, profuse perspiration, and dyspnea. He was admitted to the St. Joseph Hospital, Mishawaka, with a temperature of 104° F. When seen in consultation (A.S.G.), he appeared critically ill with a very anxious expression. The skin was pale, moist and icteric. The systolic blood pressure was 110 and the diastolic 65 mm. of mercury. Physical examination was essentially negative. His past history was irrelevant and there was no history of jaundice or anemia in the family. Careful inquiry revealed no history of contact with any dyes or special drugs. The blood showed a marked anemia and leukocytosis with evidences of regeneration and a predominance of macrocytes. The fragility of erythrocytes was not increased. The urine was highly colored and contained traces of hemoglobin. Albumen was 2+. Urobilin 4+. Urine sediment revealed occasional granular casts. The serum bilirubin was 2.8 mg. % and the direct van den Bergh reaction was weakly positive. The blood culture remained sterile. The patient belonged to Group IV (Moss) and on cross-agglutination it was discovered that he agglutinated the cells of all Groups IV, including his own cells. The specific autohemagglutination appeared at room temperature and disappeared by heating at 37° C. Because of this, the transfusion was given in gradual amounts beginning with 1 cc. of blood and gradually increased until the patient received 500 cc. of the citrated Group IV blood. This was followed by a mild immediate reaction, but the result of transfusion was phenomenal. The patient's temperature dropped and the general condition markedly improved. The worried expression disappeared. The following day intramuscular liver therapy was instituted and on November 18 the hemoglobin increased to 39% (5.85 gm. %), erythrocytes 2.2 millions, leukocytes 31,500 per c.mm. The differential count revealed no appreciable changes (Table 1). Examination of gastric juice revealed normal acid components.

The patient made an uneventful recovery and left the hospital after a stay of 19 days. He resumed his occupation and was last seen, June 19, 1936, in good health and the blood was normal in every respect. The phenomenon of the autohemagglutination persisted for 21 days and gradually disappeared.

CASE 3.—E. K., a white male farmer, aged 60 years, was admitted to the St. Joseph Hospital, Mishawaka, May 17, 1936, complaining of headaches, shortness of breath and occasional epistaxis of a few months' duration. His present illness began suddenly while working as usual on the farm. Since the onset he had been getting progressively weaker, had noticed a slight swelling of his ankles, and finally had to stop working. The family history did not reveal any history of jaundice or anemia. Physical examination on admission to the hospital revealed a well-built male, markedly dyspneic and appearing acutely ill. The skin was extremely pale with definite icteric tinge. Temperature was 102° F., respiration 22, pulse 90. The liver was palpable 3.5 cm. below the costal margin. The spleen was not palpable. On May 18, 1936, the blood picture revealed: Hemoglobin 25%, erythrocytes 1.45 millions, color index 0.89, leukocytes 7150 per c.mm. (77% neutrophils) and 3% myelocytes. Stained smears revealed considerable anisocytosis and slight poikilocytosis. Three days later, May 21, the hemoglobin was 21% (3.15 gm. %), erythrocytes 1.36 millions, color index 0.8, leukocytes 13,800 per c.mm. (94% neutrophils and 3% myelocytes). The platelet count was 250,000 per c.mm. Coagulation time was 6 minutes, bleeding time (Duke's method) 3. The urine was highly colored, the bile test negative, and the urobilin increased. The patient was treated with digitalis but did not make any improvement and expired on the fifth day after hospitalization.

Necropsy. The skin showed an extreme pallor with definite icteric tinge. Both nostrils were occluded by clotted blood. The tongue was dry and moderately coated but did not show any signs of glossitis. Lymph nodes were not palpable. On opening the body, the heart was found to be considerably enlarged with marked bilateral hypertrophy of the ventricles. The lungs were anemic and showed marked chronic emphysema. The spleen appeared slightly enlarged; its capsule contained numerous petechial hemorrhages. The liver was markedly enlarged and soft, of a chestnut-brown color with occasional light yellowish areas. The normal acinar structure was obliterated. The gall bladder was without evident lesion and the extrahepatic ducts were patent. The kidneys were normal in size and finely granular. Numerous petechial hemorrhages were present on the surface. The carefully searched gastro-intestinal tract was without evident lesion. The bone marrow of the femur was rather abundant, pinkish yellowish in color and somewhat gelatinous in consistency. Microscopic examination of the bone marrow showed a moderate but definite cellular hyperplasia involving both the erythropoietic and leukopoietic system. Section from the liver showed a marked parenchymatous degeneration, with necrosis of the liver cells surrounding the central veins. A large number of liver cells contained brownish pigment, most of which did not give the Prussian blue reaction for free iron and was apparently bile pigment. Section from the kidney showed a picture of chronic glomerulonephritis. The pathologic diagnoses were the following: (1) Eccentric cardiac hypertrophy with myofibrosis and sclerosis of coronary arteries; (1) anemia and chronic emphysema of lungs; (3) capsular hemorrhages of spleen; (4) acute parenchymatous degeneration of liver with retention of bile pigment (hemosiderosis?); (5) chronic glomerulonephritis with parenchymatous degeneration of kidneys; (6) hyperplasia of the bone marrow.

Discussion. Cases 1 and 2 present a rather typical picture of acute hemolytic anemia. The sudden onset, the rapid development of a severe anemia without an apparent cause, and the dramatic response to a blood transfusion with complete recovery are very characteristic. The highly colored, red, dark brown urine of Case 1

was most probably due to hemoglobinuria. In Case 2, the finding of hemoglobinuria was definitely established. The significance of the faintly positive van den Bergh reaction will be discussed later and it might be well to mention that this reaction was carried out by the ring-test technique (Elton[22]) which seems to give more sensitive results.

Case 2 was complicated by the simultaneous occurrence of spontaneous autohemagglutination. The autohemagglutination is an exceptional hematologic phenomenon without a grave prognosis. The small number of cases reported up to date have occurred mainly in disease associated with severe liver damage (cirrhosis, etc.) in familial acholuric jaundice and in different kinds of blood dyscrasias (leukemia, pernicious anemia, agranulocytosis, etc.). The autohemagglutination is relatively frequently observed in diseases produced by trypanosoma. This report represents the first observation of autohemagglutination in acute hemolytic anemia of Lederer. The autohemagglutination disappeared after 3 weeks and was subsequently found negative on repeated occasions under different experimental conditions (cooling in the icebox, etc.). As illustrated in our case, autohemagglutination does not bar a blood transfusion, although the serum's autohemagglutination is associated with considerable iso- and heteroagglutinating properties (Bonnard[6]). The disappearance of autohemagglutination at the temperature of 37° C. may explain why this phenomenon did not occur within the body. As to the hemolytic properties of the autoagglutinating serum, the absence of auto- or isohemolysin seems to be constant (Bonnard[6]).

While Cases 1 and 2 are typical examples of acute hemolytic anemia, Case 3 is reported as a possible case. The somewhat incomplete data available make it difficult to come to a definite conclusion, but the sudden development of a grave anemia of the normochromic and macrocytic type, the associated icterus and the fatal exitus in the absence of transfusion as well as the necropsy findings in bone marrow and liver are suggestive. The possibility of a pernicious or a symptomatic anemia as the result of the chronic nephritis were also considered but dropped for lack of sufficient evidence.

A review of the literature gave 52 cases which may be regarded as belonging to Lederer's type of acute hemolytic anemia. Some were described under other titles, on the other hand, some of those described as Lederer's anemia did not appear to fit into this rather characteristic picture.

Age and Incidence. The acute hemolytic anemia of Lederer occurs at any age with possible predilection for the first 3 decades of life. The age of the reported cases ranges from 6 months to 60 years. There is no reason to assume that Lederer's anemia does not occur in infants under 2 years of age as suggested by O'Donogue and Witts.[52] In fact, Lederer himself reported 2 cases in babies

6 and 16 months of age.[39a,b] Both sexes seem to be equally affected. The scanty material available to date makes it difficult to make a definite statement as to the frequency of its occurrence; but there is considerable evidence to assume that this form of acute anemia is not a rarity but a disease of rather frequent occurrence.

Clinical Picture. The onset in typical cases is sudden, without any previous history of anemia or jaundice. Upper respiratory infection or sudden onset of general weakness and headaches or digestive disorders (vomiting or diarrhea) are frequent beginnings. An attack of abdominal pain may be an initial symptom simulating appendicitis (Parkes Weber[71]). Some atypical cases exhibit a subacute onset with prodromal symptoms such as: progressive fatigue, shortness of breath, occasional epistaxis, etc. After an incubation period of 2 to 6 days, a severe anemia develops accompanied by intensive pallor, icterus of varying degrees and a rise of temperature. The patient presents a picture of acute and critical illness with approaching coma or prostration. The air hunger, no doubt due to an acute anoxemia, is common. The temperature varies. In most cases there is a mild pyrexia, but temperatures of 104° F. are not infrequent. Physical examination reveals in some cases splenic and in others hepatic enlargement. The clinically demonstrable splenomegaly, however, does not necessarily belong to the picture of this disease. Occasionally cardiac manifestations are present (Manne and Kuskin[46]) and hemic murmurs are frequently observed. Gastric analysis usually shows normal quantities of free hydrochloric acid and there is no evidence of Hunter's glossitis. The course is rapid and tends to a complete recovery or death within a short time. The rapidity of onset, course and recovery is so characteristic for this form of anemia that the French call it *anemie en coup d'archet* (Fiessinger, Decourt and Laur[23]).

Hematology. The blood picture is characterized by rapid drop of erythrocytes and hemoglobin with appearance of immature and reticulated red blood cells with marked tendency to macrocytosis. The red blood count is usually below 2,000,000 and may be as low as 780,000 (Lederer[39a]) or 600,000 per c.mm. (Manne and Kuskin[46]). There is a pronounced anisocytosis, polychromasia, basophilic stippling and occasionally slight poikilocytosis. Cabot's rings are observed (Parsons and Hawksley,[56] Goudsmit[27]). There are usually many nucleated red cells and the presence of megaloblasts is emphasized by Lederer.[39b] O'Donogue and Witts[52] denied in their paper the occurrence of megalocytes in Lederer's anemia, although in discussing some of the reported cases they mentioned that "nucleated red cells are usually present often in large numbers and typical megaloblasts can be distinguished among them." On the other hand, Parsons and Hawksley[56] are of the opinion that the anemia of their cases has constantly been of the megalocytic type, as shown by the high color index and the presence of megaloblasts and megalo-

cytes in the peripheral blood. We believe that the tendency to macrocytosis together with the presence of many microcytes and rare poikilocytes is an important differential diagnostic point.

The marked regenerative activity is indicated by the presence of many reticulocytes, and nucleated red cells. The reticulocytosis may be as high as 64% (Fiessinger[23]). The fall of the hemoglobin and of the red cells is usually proportional, but variations of the color index above and below unity are rather frequent. Lederer's anemia belongs generally to the normochromic type.

The anemia usually is associated with marked leukocytosis and often with a leukemoid reaction (Krumbhaar[35]). The leukocytes may reach as high as 132,800 as in the case of Teeter.[65] In Lazarus'[38] case leukocytes were 108,000. O'Donogue and Witts[52] found in 12 of the 36 collected cases white blood counts ranging from 20,000 to 50,000 per c.mm. The 6 cases reported by Lederer himself showed a leukocytosis from 20,000 to 81,000 per c.mm. A marked leukocytosis was also present in our 2 cases (42,000 and 45,000). The large numbers of nucleated red cells, which are so frequently present, have probably led in some cases to an erroneous estimation of the number of leukocytes. The possible counting of erythroblasts together with leukocytes also explains some unusual variations in the number of leukocytes in some of the reported cases (Eimer,[21] Corelli[14]). Lederer[39a] was apparently aware of that fact and suggested that correction should be made by subtracting from the total number of cells per c.mm., as estimated by the white blood pipette, the erythroblasts as estimated in the stained preparations. The leukocytosis is mainly due to neutrophils with a varying absolute shift to the left and the appearance of immature granulocytes. In Teeter's case[65] 10.75% of the white blood count of 132,800 were myelocytes and in our second case, the myelocytes constituted 10% of this white blood count of 45,000. In 1 of the cases of Parsons and Hawksley[56] the immature leukocytes of the granular series reached 30% of a white cell count of 35,000. This leukemoid reaction is an evidence of the simultaneous involvement of the leukopoiesis by the same etiologic agent and constitutes according to our opinion a characteristic feature of acute hemolytic anemia.

Occasionally, otherwise fairly typical cases, fail to show an appreciable leukocytosis (Joules and Mastermann,[32] Altmann,[2] Holst[30] and others). Even the occasional occurrence of leukopenia and agranulocytosis is reported (Brill,[7] Opitz,[53] Manfredini,[45] Goudsmit,[27] Planteydt.[60] In the case of Planteydt, the white blood count varied from 1710 to 3400 with 1 to 14% segmented leukocytes. The monocytes were not increased. The acute hemolytic anemia occurred here following a rheumatic infection which was treated with salicylates. In the case of Goudsmit[27] the white blood count was 1400 with 21 to 53% segmented leukocytes.

Hemolysis. Excessive destruction of the red blood corpuscles is a dominant feature in this form of anemia. Since we are unable to observe and measure the hemolysis as it occurs *intra vitam*, we must rely on indirect evidences. What are the evidences of hemolysis? The following are the most important:

1. *Hyperbilirubinemia.* Hyperbilirubinemia is a certain sign of hemolysis provided liver damage or obstruction to bile flow can be excluded. The quantitative determination of bilirubin in serum by means of the van den Bergh reaction needs a few remarks. There is considerable confusion in the literature on this point and the significance of the van den Bergh reactions has often been misinterpreted. Many reports on Lederer's anemia mention that the "indirect" van den Bergh reaction was positive. The mere statement of a positive "indirect" van den Bergh reaction is of no practical diagnostic significance. This "indirect" reaction, that is the test for small quantities of bilirubin in serum by means of an alcoholic extraction, is positive in most normal serums. This reaction is just a method for quantitative determination of bilirubin. The normal serum contains less than 0.25 mg. %. In Lederer's anemia it was found in amounts to 3.3 mg. % and higher (Holst[30]). The presence of bilirubinates in serum gives the characteristic direct van den Bergh reaction which has definite diagnostic significance of liver damage. The finding of a considerably increased level of bilirubin in serum together with a negative or faintly positive direct van den Bergh reaction is suggestive of increased hemolysis. The hyperbilirubinemia in acute hemolytic anemia is partly due to excessive destruction of red blood corpuscles and partly to a definite liver damage on the basis of anoxemic necrosis resulting from the severe anemia (Rich[62]).

2. *Increased Excretion of Urobilin in Feces and Urine.* Urobilin (hydrobilirubin) is a derivative of the blood pigment and formed chiefly in the intestines. Its markedly increased excretion in the feces may be taken as evidence of excessive blood destruction within the circulation. Although the urobilin excretion does not parallel the blood destruction, its quantitative estimation in the feces is of importance in establishing a rough index for the rate of blood destruction. In the presence of an increased excretion of urobilin in feces, there is also an increase in the urine. If not due to excessive hemolysis, the urobilinuria is said to indicate some liver damage, that is, its incapacity to reconvert the reabsorbed urobilin into bilirubin. Urobilinuria and markedly increased excretion of urobilin in feces is commonly observed in acute hemolytic anemia. Lederer[39a] reported a dilution value of 104,000 for urobilinogen and 240,000 for urobilin in feces (as against 6000 to 9000 dilution value as the upper normal limit).

3. *Hemoglobinuria.* In excessive hemolysis the unmodified blood pigment without the blood cells appears in the urine. In these cases

the reticulo-endothelial system is unable to transform the large quantities of freed hemoglobin into bilirubin and unmodified hemoglobin is excreted by the kidneys. In most of the acute cases of Lederer's anemia there is hemoglobinuria. Lederer[39b] reported its occurrence in 2 instances. Parkes Weber[70] described his case as a "severe acute hemoglobinuria" and in the case of Castex, Steingart, and Poletti[9] the hemoglobinuria was the dominating symptom of more than 1 week's duration.

4. *Abnormal Increased Blood Regeneration.* The highly increased regenerative activity of the hematopoietic system is evidenced by the presence of an excessive number of reticulocytes and a large number of erythroblasts in the circulation. This reaction is no doubt the normal response of the hematopoietic system to supplement the sudden loss of erythrocytes. The tendency to put out immature red blood cells is very marked in some of the observed cases. Fiessinger[23] found 3 to 5% of the erythrocytes to be normoblasts and Castex[9] counted as many as 11,400 nucleated red cells per c.mm. Among them, 30% were normoblasts and 20% megaloblasts. In Teeter's case[65] there were 20,000 erythroblasts per c.mm.

5. *Fragility of the Erythrocytes.* Increased fragility suggests inherently weak cells (particularly in congenital hemolytic icterus); but, of course, a marked hemolysis may be present without any change in the resistance of the erythrocytes. In fact, our present knowledge does not afford any definite relation between the resistance of red blood cells to hypotonic salt solution and hemolysis as it occurs within the body. The resistance of red blood cells in acute hemolytic anemia is as a rule normal, but may be lowered in the active phase of anemia (Fiessinger,[23] Parsons and Hawksley,[56] and Lewis[42]).

Diagnosis. The correct diagnosis of acute hemolytic anemia may present some difficulties; yet its recognition is of great practical importance in regard to prognosis and treatment. The diagnosis is based on the acute onset; rapid development of a severe anemia without any obvious cause; evidence of hemolysis; marked leukocytosis; macrocytic type of blood regeneration with marked reticulocytosis. The differential diagnosis includes: pernicious anemia, acute leukemia, congenital hemolytic icterus, erythroblastic anemia, "pernicious" anemia of pregnancy, simple achlorhydric anemia, aplastic anemia, and miscellaneous infectious diseases. Acute leukemia may be one of the most important and at the same time one of the most difficult of the differential diagnoses. The leukocytosis may in some true cases of Lederer's anemia be so marked as to present a leukemoid reaction. Many true cases of acute hemolytic anemia were thus misinterpreted as acute leukemias with recovery. Teeter's case[65] of a 6-year-old girl, suddenly taken ill with fever, vomiting and a severe anemia, is no doubt a typical case of acute hemolytic anemia. On the other hand, Parsons and Hawksley[56]

described a case in a boy, aged 4, which appeared to be a fairly typical acute hemolytic anemia with recovery. Three weeks after the supposed recovery the boy was found to be suffering from acute lymphatic leukemia. The diagnosis of acute leukemia was confirmed at necropsy.

Hemolytic crisis in unsuspected familial acholuric jaundice may closely simulate Lederer's anemia. An illustrative case of this kind is described by Murray-Lyon.[49] Increased fragility would be an important differential feature in such cases.

Some authors have attempted to identify the acute hemolytic anemia of Lederer type with the so-called "pernicious" or "hemolytic" anemia of pregnancy (Witts[75]). A great deal of evidence, however, speaks against this. Clinical observations suggest an intimate connection of the "pernicious anemia of pregnancy" with the mere fact of gestation. Many authors report the recurrence of anemia in subsequent pregnancies. Considerable evidence has been accumulated which justifies the assumption that the hyperchromic anemia of pregnancy is primarily due to a deficiency, probably of the antianemic substance and that the hemolytic destruction of the red blood cells is secondary. In India, where this form of pregnancy anemia is frequent and often fatal, it has been possible to establish a relation between it and the general nutrition, and to cure this anemia not only by liver extracts, but also by extracts of yeast (Wills[73,74]). Both liver and yeast are known to possess large quantities of vitamin B. Ottenberg[54] classifies this "pregnancy pernicious anemia" among those due to a deficiency of the antianemic principle. As to the hematology, the blood picture may be identical with that of a true pernicious anemia. A leukocytosis is usually absent. The reticulocytosis is not marked in this anemia of pregnancy and only few normoblasts appear in the circulating blood.

For further differential diagnosis of anemias see the self-explanatory Table 2, in which only the most characteristic features are tabulated.

Prognosis. The prognosis of untreated Lederer's anemia is grave, but it is absolutely favorable when proper treatment is given at the right time. It seems that it also possesses some tendency to spontaneous recovery (Lewis[42] and others).

Treatment. The treatment of choice is blood transfusion. The response to a single transfusion is often dramatic, followed by a complete recovery. Some authors believe the transfusion to be "specifically curative" (Ottenberg[54]). In a few reported cases in which the death occurred in spite of blood transfusion, if the correct diagnosis is not to be questioned, we believe that transfusion was delayed until too late. One case is described where a severe rigor followed transfusion, with death occurring 3½ days later (Payne[58]). Necropsy revealed massive "hemoglobin infarction" of the kidneys.

TABLE 2.—DIFFERENTIAL DIAGNOSIS OF ANEMIAS

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Disease	Onset	Erythrocytes.									Leukocytes.	Bilirubin in serum.	Free HCl.	Other characteristics.
		Hb. content.	Size and shape.			Blast forms.		Staining qualities.		Reticulocytes.				
			Size.	Aniso.	Poik.	Normo.	Meg.	Poly.	B.St.					
Acute hemolytic anemia	Acute	Usually normo- or hyperchromic	Macros., ++ Micros., +	+++	±	+++	+	+++	++	+++	Great incr ; shift to left; leukemoid reaction	++	+	Rapid onset and course; recovery or death; fever.
Pernicious anemia	Slow, progressive	Hyperchromic	Megalos.	++++	++++	+	+	+	+	After liver +++	Leukopenia; shift to right	+	−	Tend. to remissions; response to liver therapy.
Acute leukemia	Acute prodromal symp.	Variable	Normos.	++	++	++	+	++	+	++	Incr. or decr.; immaturity	+	+	Tend. to hemorrhage; fever; fatal course.
Spherocytic jaundice (congenital hemolytic icterus)	May be acute (crisis)	Normochromic	Micros. (spherocytes)	+	±	±	−	+	−	++++	Normal	+	+	Predom. spherocytes; incr. fragility; hemolytic crisis; splenomegaly; fam. hist.
Erythroblastic anemia	Acute	Normo- or hyperchromic	Macros., ++ Micros., +	+	+	++++	−	+	++	+++	Mod. incr.	+++	+	Racial incid.; bone involv. of skull and digits; mongolian facies.
Pernicious anemia of pregnancy	May be sudden	Hyperchromic	Macros.	+++	+++	+	+	+	+	After liver ++	Nor. or mod. incr.	+	+	Assoc. with preg.; compl. recovery with treat.
Simple achlorhydric anemia	Subacute or chronic	Hypochromic	Micros.	++	++	±	−	−	±	+	Normal	−	−	Characteristic response to appropriate treatment.
Aplastic anemia	Acute	Normochromic	Normos.	+++	+++	−	−	++	++	−	Leukopenia	−	+	Progressive fatal course.

Abbreviations: Aniso. = Anisocytosis; Poik. = Poikilocytosis; Poly. = Polychromatophilia; B.St. = Basophilic stippling.

It appears to us questionable whether it was a true case of Lederer's anemia. The subacute onset, the absence of the nucleated red cells in the circulation, the normal Price-Jones curve of the red cell diameters and the necropsy findings do not seem to confirm this diagnosis.

The exact effect of blood transfusion is still an open question. Some authors believe that it causes a stimulation of the bone marrow (Morawitz,[47a] Deneke,[17] Leicik[41]). Anders[3] and Nather and Hickl[50] believe that the action of the transfused blood is not limited to the stimulation of bone marrow but that it also stimulates the antihemolytic property of the blood. According to Gross and Gratz,[29] the serum acts as in foreign protein therapy, having a stimulating action on the cytoplasm in general, while the red blood corpuscles act as transplanted cells. Kallius[33] believes that the favorable results of blood transfusions are due not to the transfused cells but to the serum. Curschmann[15] suggests that transfusion is a true substitution therapy, rather than a stimulating therapy and that transfusions relieve the bone marrow from an added load, thus causing a diminution of reticulocytes. Kühl[36] explains the action of transfusion on the basis that at first the entire hemolytic system has been blocked by the transfused blood, thus saving the red blood corpuscles of the patient from further hemolytic action. Secondly, the products of transfusion have a stimulating action on the bone marrow causing an elevation of red cells due to the bone-marrow reaction. Manfredini[45] essentially agrees with this point of view. We are inclined to assume with Kühl[36] and Manfredini[45] the importance of the antilytic action of the transfused blood. The transfused blood may contain an unknown substance which neutralizes the stimulating effect on the reticulo-endothelial system and stimulates the liver to produce the antianemic principle. The latter brings about maturation of the young cells. Thus the quick effect of transfusion may be explained. The transfused blood possibly also acts by checking the etiologic infectious agent.

As to the efficiency of the liver therapy in acute hemolytic anemia of Lederer, a considerable divergence of opinion prevails among the authors. Some found no response to the liver and regard this as an important differential point from pernicious anemia (Christiansen,[11] Joules and Mastermann[32]). Other authors seem to have obtained favorable results with liver injections (Benhamou,[4] Fiessinger,[23] Corelli,[14] Vedel[69]). The subject needs further investigation.

Pathologic Anatomy. The pathologic findings described so far in a relatively small numbers of necropsies do not present any particularly characteristic features other than evidences of severe anemia without an obvious cause. The liver, spleen, and kidneys generally give the Prussian blue reaction for free iron. The spleen is moderately enlarged and may show sterile infarcts. The liver is usually

more markedly involved showing varying degrees of acute parenchymatous degeneration with necrosis around the central veins. Rich,[62] in a histologic study of livers associated with anemia of all kinds, noted that necrosis of liver cells in the central portions of each lobule was a constant finding and proportional to the degree of anemia. The cause of this lesion is postulated to be due to an insufficient number of oxygen-carrying cells (anoxemia). Similar changes in the liver have been produced experimentally by subjecting animals to low barometric pressures and low oxygen tension.

The bone marrow is usually hyperplastic, "maroon colored or like red-currant jelly" (O'Donogue and Witts[52]). But occasionally in cases coming to necropsy the bone marrow may show some aplastic changes (Eimer[21]).

Moschcowitz[48] found in his case of acute febrile pleiochromic anemia hyaline thrombosis of the terminal arterioles and capillaries. This was particularly marked within the heart muscle. Whether his case truly belongs to Lederer's form of anemia appears somewhat questionable. Lederer[39b] himself failed to see a resemblance.

Pathogenesis. We have described acute hemolytic anemia in its clinical, hematologic and pathologic manifestations and now have to raise the question as to its pathogenesis and position in the hematologic system.

We believe with most of the authors that there is sufficient evidence to justify consideration of Lederer's anemia as a "Hemolytic Anemia." Ottenberg[54] in his new classification of anemias gives to Lederer's anemia an independent place among anemias due to toxic destruction of blood by infections. Similarly Vaughan[68] classifies it as an "unexplained hemolytic anemia." A few authors, however, consider it the result of a disturbance in the formation of red blood cells, which by their vulnerability are destroyed in great numbers (Goudsmit[27]). In this conception, we do not clearly see how to explain plausibly all the suddenness and rapidity of onset, course and recovery, which is so characteristic for this type of anemia.

A few authors regard acute hemolytic anemias as clinical varieties of pernicious anemia (Greppi and Semenza,[28] Campanacci).[8] They describe cases with subacute or acute onset and a clinical picture resembling Lederer's anemia with recovery following transfusion and liver therapy. A striking feature in all these cases is the absence of free hydrochloric acid in the gastric contents associated with a leukopenia and tendency to mononucleosis. These features, characteristic for pernicious anemia, do not belong to the picture of acute hemolytic anemia. Troisier, Bariety and Brocard[67] reported a similar case which showed still more resemblance to pernicious anemia. There was a total achlorhydria even after histamine injection, the tongue resembled Hunter's glossitis and the leukocytes numbered 2000 to 3000 with 3 to 10% myelocytes and 32 to 40%

neutrophils. These cases may indeed represent typical febrile variations of pernicious anemia with long remissions obtained by liver therapy but it is entirely unjustified to draw from these observations the general conclusion denying the existence of such an entity as acute hemolytic anemia of the type Lederer and considering it a variation of pernicious anemia.

The infectious origin of acute hemolytic anemia is very suggestive, but attempts to cultivate a microörganism from these patients have completely failed so far. All blood cultures remained sterile. If we recall the extrinsic factors that may produce acute hemolytic anemias, we have to mention in addition to the chemical poisons certain foods and microörganisms. Among the foods there are certain kinds of hemolysis producing mushrooms and there exists in Italy a peculiar disease characterized by severe anemia of hemolytic type, which is due to ingestion of a kind of bean ("Favismo"). Among the microörganisms *B. welchii* and the hemolytic streptococcus are the most important.

Bartonella infection, in man known as Oroya fever or verruga peruviana,[34] presents several interesting features which justifies our brief consideration. Oroya fever, most commonly encountered in the western Andes, is an acute infectious disease characterized by extremely severe hemolytic anemia of the hyperchromic megalocytic type accompanied by fever and considerable leukocytosis. The causative organism, first observed by Barton in 1904 and isolated by Noguchi in 1926, is the so-called Bartonella bacilliformis which is now regarded as a bacterium. It belongs to a group of microörganisms, the parasitic nature of which has been proven during the last few years (Kikuth[34]). A remarkable feature of this acute Oroya fever anemia is that it has, like the acute hemolytic anemia of Lederer, the tendency to spontaneous recovery without specific treatment. Can we not recognize some interesting parallels between Oroya fever and acute hemolytic anemia of the Lederer type? In future studies and observations on Lederer's anemia, the blood smears should be carefully investigated for possible bacteria-like inclusion bodies within the red blood cells.

The clarification of the etiology of the acute hemolytic anemia (Lederer type) will help to establish a definite independent place for this form of anemia in the hematological system. It already exists as a clinical and pathologic entity.

Summary. 1. Three cases of acute hemolytic anemia (Lederer type) are reported and the literature reviewed.

2. The general picture of the disease is drawn and the differential diagnosis discussed.

3. Acute hemolytic anemia is characterized by an acute onset with fever, rapid development of a severe anemia with the appearance of immature cells, marked reticulocytosis and leukocytosis and tendency to complete recovery. The dramatic response to a single

blood transfusion appears to be very characteristic. The anemia is usually of the normochromic type with marked tendency to macrocytosis.

4. It is suggested that acute hemolytic anemia is not a rare occurrence and that many cases of obscure anemia reported in the literature as well as reports on recovery from acute leukemia actually belong to this group.

5. The clinical recognition of Lederer's anemia is of greatest practical importance since the untreated disease has a high mortality rate while the prognosis of the treated disease is absolutely favorable. Blood transfusion is the treatment of choice.

6. The reported occurrence of spontaneous autohemagglutination in course of acute hemolytic anemia is observed for the first time.

7. Some theories as to the action of blood transfusion are briefly presented.

8. The etiology of acute hemolytic anemia is at present unknown but its infectious nature is very strongly suggested. A comparison with the acute hemolytic anemia of Oroya fever is made.

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SKIN IRRITATION AND CANCER IN THE U. S. NAVY.*

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The object of the study is to ascertain first, whether a group of adults between 16 and 45 or 50 years of age, exposed intensively to open air, to sun rays and to salt water suffer from skin and lip cancer more than the average. Second, whether or not this group shows the same probability of dying from cancer of the inner organs as does the general population. Third, whether or not young men cured of a skin or lip cancer are later as much disposed to cancer of the inner organs and of the surface as men of the same age group.

These problems are important from the points of view both of the pathogenesis of cancer and of public health. Roffo[2] showed in systematic animal experiments the significance of ultraviolet rays in the genesis of skin cancer. He thereupon warns against too much sun bathing. It is also known, that in rural districts epitheliomata of the skin and lip are more frequent than in the cities. Whether there are any differences in the incidence of the inner cancers is not known, because of the quality of the reports of causes of death in rural areas.

* The publication has the approval of the authorities of the U. S. Navy.

The conditions in the Navy represent an experiment on human beings. The results of the experiment were studied on the histories of cancer collected in the Bureau of Medicine and Surgery of the U. S. Navy.

The morbidity and the mortality was calculated for the 8 years 1929 to 1936,* the figures so obtained being based on 875,000 person-years of active service. The observations regarding the distribution of cancer according to the organ and age were based on 469 cases.

Skin and Lip Cancer. Both the morbidity and the mortality of skin and lip cancer are very high. Among 100,000 active males—officers and men—there occurred annually 8.9 ± 1.0 new cases of skin or lip cancer (actually 78 cases), and there were 1.25 ± 0.39 deaths from each of these two types of cancer. Thirteen cases for which the onset of the illness was before 1929—either another primary tumor of the same organ or as the same tumor—are *not* included in the above calculation of morbidity. The mortality figure contains all cases with an onset of the illness during the active service.

The 11 deaths from skin and lip cancer occurred among the active, reserve and invalided. Two deaths with an onset of the carcinoma after the men were transferred into the reserve, are here not counted.

It may be of interest, that among the 9 fatal cases of skin cancer between 20 and 49, 5 cases were melanomata, whereas among the non-fatal cases melanoma was infrequent (only 1 case).

Applying the skin and lip cancer age specific death rates from the general mortality statistics of U. S. A.† to the particular age distribution of the total group of males in active service in the U. S. Navy, there would be expected 3.56 deaths from skin and lip cancer instead of the observed 11. The mortality from skin and lip cancer in the Navy was thus in 1929–36 about 3 times higher than in the civil population of comparable ages in the U. S. A.

In spite of the large probable error, the higher mortality from skin and lip cancer is by no means accidental, as is seen from the high morbidity, which is also, with due regard to the probable error, much higher than in the civil population.

The personnel of the Navy is continuously under intensive medical supervision. All modern diagnostic and therapeutic achievements are at their disposal. There are yearly thorough preventive examinations. Under these circumstances, the therapeutic results should be much better than in the civil population, at least so far as skin and lip cancer are concerned.

According to our figures the relation between the admitted and the fatal cases of cancer of skin and lip was in the years 1929–36 as 7 to 1 and 8 to 1 respectively,‡ whereas the same relation in the

* Exactly 7 years and 11 months, from January 1, 1929, to November 30, 1936.

† Skin + scrotum + lip. Skin, 1927–33; scrotum and lip, 1930–33.

‡ From Table 1, 2 *b* or 2 *a* and *b*.

civil population is according to clinical experience between 2 to 1 and 3 to 1.

TABLE 1.—CANCER OF THE SKIN AND LIP.

1. U. S. Navy, active males; person-years of observation, 1929–36	875,000
2. Cases of cancer of the skin and lip with the onset	
(*a*) Before 1929 and during active service	13
(*b*) 1929–1936 and during active service	78
3. Deaths (skin and lip) during 1929–1936 due to:	
2 *a*	6
2 *b*	5

A ratio of 50% cured cases indicates that the morbidity is twice as high as the mortality; a curability of 66.6% means that out of 3 ill cases 1 dies and 2 survive, and from a ratio of about 86% we learn that each death corresponds to 6 survivors.

Considering that the therapeutic results were much better than in the civil population and that in spite of this the mortality from skin and lip cancer was higher, it is concluded that the morbidity in the Navy is according to the next calculation (Table 2) about 7.5 to 9 times higher than in the civil population and about 22 times higher than the mortality from skin and lip cancer in the civil population of the same age distribution. The figures are so surprising that it is necessary to point out that in 70% of the cases the diagnosis was proved by biopsy, necropsy or death, and that in a certain part of the other cases the clinical history and the authorities in the American medical world who treated them are a guarantee that there was no mistake.

TABLE 2.—SKIN AND LIP CASES.

Skin and lip cancer.	U. S. (civil males) of the same age distribution as U. S. Navy active persons.	U. S. Navy
If the mortality per 100,000 is	*a*	3.14 *a*
and		
the per cent of cured cases is	about 60 to 66.6	86
the morbidity per 100,000 is	2.5 *a* to 3 *a*	$7.1 \times 3.14\,a = 22.4\,a$

The Total Cancer Mortality. The total cancer mortality in the Navy was in the years 1929–36 very low. The age specific death rates are mostly even smaller than the official death rates of white males in the Registration Area of U. S. A., which reveal—as is well known—only a part of the real cancer mortality. The deficit of cancer deaths in the Navy is therefore very considerable.

During 1929–36 (up to November 30, 1936) there occurred in the Navy (a) 112 cancer deaths* belonging to persons on duty or to persons which at the onset of the illness were on active duty; (b) 202 cancer deaths† belonging to the inactive personnel, with the onset of the illness in the period of inactivity; (c) 3 cases of malig-

* In 102 cases a postmortem examination was performed.

† In 127 cases a postmortem examination was performed, in most of the other cases the diagnosis was proved by biopsy, operation or Roentgen rays.

nancies, one osteosarcoma, one of myxosarcomata and one melanoma which became invalided and up to now could not be followed up. They may be dead. Today we can only calculate the death rates from the active personnel (875,000 person-years of observation) and we hope to be able to extend this part of the study to the inactive group.

Table 3 illustrates the real and the calculated number of deaths by applying the age-specific cancer mortality rates of males in U. S. Registration Area for 1928–1932, and in New York City for 1920 to a population of the same size and age structure as the Navy. It is probable, that by applying the figures from New York or Chicago or Baltimore and so on from a more recent date, the deficit of cancers would be even larger than calculated here. On the other hand, it must be considered that in the population of New York in each age group itself the number of older people is relatively larger and of younger smaller, than in the Navy. Thus the real difference may be as large as in the table or even a little smaller than in Table 3.

TABLE 3.—REAL AND CALCULATED NUMBER OF CANCER DEATHS IN U. S. NAVY, ACTIVE PERSONNEL, 1929–1936.

Age, yrs.	Person—years of observation.	Actual deaths in the U. S. Navy.	Calculated deaths by applying the age specific death rates of white males from: U. S. Registration Area, 1928–32 to the actual number of observed years in the Navy.	Calculated deaths by applying the age specific death rates of white males from: New York City, 1920 to the actual number of observed years in the Navy.
16–19	79,900	3	3.3	3.4
20–24	321,030	14 (+ 2?)*	17.0	16.0
25–29	195,900	13 (+ 1?)*	15.4	47.8
30–34	141,800	16	18.0	
35–44	109,680	31	33.1	55.3
45–54	23,375	26	24.6	44.3
55–64	3,300	10	8.9	17.8
Total cases	...	113 (+ 3?)*	120.3	184.6
Skin and lip	...	11	3.5 less than	5.0†
Without skin and lip	...	102 (+ 3?)*	116.8	179.6
Mortality per 100,000	...	11.6 ± 1.0	13.3	20.4 ± 1.5

* The cases which could not be followed up.
† Not exactly known.

The first enlistment examination has certainly a selective effect and does eliminate persons with symptoms of serious illness, thus diminishing also the rate of cancer mortality in the immediately following years, *i. e.*, in the age groups 16–19 and 20–24. But in this group there seems to be no deficit at all. There appear to be no measures which could artificially diminish the incidence of

cancer among the personnel in the age groups 24–64. Therefore these differences have to be considered as real.

According to our calculation 44% of the expected deaths are lacking, in absolute figures: 78 or 75* cases. Nobody will think that this higher difference is due to better results, and it is not. (In another paper we shall deal with this question.) But it must be remembered that we have in this population in the same years of observation about 80 cases of skin and lip cancer more than were expected. The close numerical relation between the actual hypermorbidity of the skin and lip on the one hand and the hypomortality of all other cancers from the other, is striking.

Astonishing as these results may seem, they are in agreement with Peller's[1] previous results.

The diminished cancer mortality is not accidental: It appears rather to be the consequence of biologic changes due to the increased skin and lip irritation by factors that are not cancerogenous for the inner organs. Thus the number of curable tumors on the surface becomes more frequent, but at the same time the number of the inner tumors, which are in most cases fatal, becomes smaller. This diminishes the total cancer mortality *and saves the lives of a certain number of people.* At this moment it is not important, whether all the 44% were saved by the peculiar interference of the skin and lip, or only for instance 34%, the other 10% relying upon other factors (among them therapy). It is also not known whether the lives are saved forever from cancer or whether they will die later from another cancer. Unfortunately, it is until now impossible to calculate the mortality for higher ages of the inactive personnel of the naval reserve, which has an age distribution more favorable for attacking this problem. (Of 207 death cases in the reserve 163 died between 50 and over 90.)

The Ratio of Skin and Lip Among All Cancers. For all available mortality statistics only about 5% of the male cancer deaths were credited to the skin and lip, the percentage being smaller among young adults and rising in the higher age groups. In the U. S. Navy the situation is very different.†

In the Navy deaths from skin and lip cancers were in younger years relatively more frequent than later. The ratio of skin and lip thus drops from the high level at 20–49 to a low level at 60–69 in which age the per cent of skin and lip cancer is almost as high as in the general population.

The explanation is not difficult. In the age groups 20–49 the personnel of the Navy is more exposed to skin irritations than later,

* If the 3 cases which could not be followed up are also dead, then 42%, or 75 cases, are lacking. While this paper was in press 5 of these 7 cases were followed up; 1 of the 5 had died.

† This part of the study is based on 469 fatal cancer cases, partly from the years 1929–1936, partly from earlier years.

where a large part, being in the reserve, are not more exposed to the sun and other skin irritations than the civil population of the same ages.

TABLE 4.—AGE DISTRIBUTION OF CANCER MORTALITY.

Age, yrs.	Total number of cancer deaths.	Deaths from skin and lip cancer.			U. S. A., ratio of skin and lip cancers (in per cent of all cancers).
		Absolute.	In per cent of all cancers.		
15–19	7	..	....		3.2
20–39	125	13	10.4	9.0±1.9	3.2
40–49	97	7	7.2		3.2
50–59	97	4	4.1		3.2
60–69	83	3	3.6		3.8
70 and over	60	3	5.0		7.7

It is possible that all or a part of the older men, who in younger years were cured of a skin and lip cancer, might have in the ages above 60 produced a new primary tumor in the inner organs, because their skin or lip cancer which was provoked 20, 30, 40 or 50 years ago did not any longer protect them. Until now this problem has not been studied, neither systematically nor occasionally. But as the skin ratio in the age groups 60–69 and over 70 is not exceptionally low—it is almost normal—the mentioned supposition is not probable.

The Multiplicity of Primary Tumors Resulting From a Cured Former Cancer of Skin or Lip. Among our fatal internal cancer cases there were found 3 cases with a cured malignant growth on the surface before the inner malignancy, *viz.:*

1. 1916, a 52-year-old man, epithelioma of the skin between the eyebrows on the roof of the nose; Roentgen ray treatment; cured.—Seventeen years later (1933) he died from a squamous-cell carcinoma of the nasal septum.

2. 1926, a 66-year-old man, epithelioma of the skin, left cheek; Roentgen ray treatment; 1927 a recurrence, surgical treatment; 1929 a tumor mass sub-diaphragmatically located by roentgen ray; 1930 pains in epigastrium, difficulties of swallowing. In April, 1931, he died from carcinoma of the esophagus.

3. 1929, a 69-year-old man, epithelioma of the skin on the left arm; excised in June, 1929.—In September, 1930 ($1\frac{1}{4}$ years later) he died from a cancer of the lung.

It must be admitted that the third case is a very doubtful one. It is probable that the lung tumor existed longer than 14 months and that both the lung and the skin tumor were synchronous. It is well known that a part of the inner tumors exist for a long time without any clinical symptoms, being detected only accidentally or terminally.

Among the cases of fatal malignancy there were many cases with a previously treated *benign* tumor on the skin and also 2 cases with a small ulcer on the lip, which was suspected to be an epithelioma but proved to be benign. One, a fatal cancer of the tongue, had 7

years previously (at the age of 43) an ulcer on the lower lip, which was excised and showed histologically *no* evidence of malignancy. The other case, a person with carcinoma recti (aged 54 years) had 5 years previously a small fissure on the lip, which according to the consulting specialist was benign and healed under ultraviolet ray treatment.

We have not mentioned until now the cancer cases in the nursing corps of the U. S. Navy. They form a small group, not suitable for a statistical analysis. There are altogether 14 nurses with a cancer. In 7 cases it was a cancer of the breast, in 1 a cancer of the uterus. One of the 7 breast cases is of casuistical interest, representing a multiplicity of tumors in a combination seldom found in women.

In February, 1933, a 42-year-old woman with squamous-cell carcinoma of the breast, had mastectomy;—15 months later (May, 1934) hysterectomy because of uterus myomatosus. During the operation an adenocarcinoma (Grade III) of *both* ovaries was revealed; 4 months later a fibroadenoma of an accessory breast was excised.

In this as in the cases which are interesting from our point of view it must be remembered that according to clinical experience a case is classified as cured, only after an interval of 5 years without symptoms. It is impossible after 1 or 2 or 3 years to say that a patient is cured, even if he seems to be. It is also impossible to decide whether in the last quoted case (breast-ovary) the tumors were synchronous or metachronous. Evidently synchronous tumors are, it may be repeated, of no interest to us; therefore we did not mention them, in spite of the fact that they are also represented in our material. One of these cases of synchronous multiplicity showed the combination surface—inner organs (cancer of the lip and of the larynx).

In none of the internal cancers with an onset of the illness between 30 and 50 the history showed a previously cured skin or lip cancer.

Unfortunately, the histories in a larger part of the older cases are incomplete. They were not kept. Thus the material we may turn to account is small. In only 115 cases over age 50 is the calculation possible. Among these cases we found the quoted 3 cases with a previously cured skin or lip cancer. The expectation was sometimes higher. We should not forget that the material is too small to make definite calculations. A research on a large scale is necessary. But even if the difference between the real and expected figure would shrink, the question we have to study would be: how long do the cases live between the first and the second tumor?

Summary. 1. The peculiar conditions of life in the U. S. Navy—the prolonged exposure to the sun's rays, to open air and to salt water—are associated with (*a*) a skin and lip cancer frequency 8 times normal, and (*b*) a greatly diminished morbidity and mortality from all other cancers. About four-tenths of the men who would be

expected to die from an inner malignancy produced instead of this cancer a curable skin or lip tumor.

2. The mortality from skin and lip cancer is in the U. S. Navy about 3 times higher than in the average population (of the same age composition). Among the fatal cases melanoma predominates. The danger from epitheliomata is small.

3. It seems that only a small part of the cured skin and lip cancer patients produce later a tumor in the inner organs. This problem must be studied on a larger scale.

4. By exposing young men to strong skin irritations which are not carcinogenous to inner organs, the lives of some who would die from a cancer might be saved, at least for a certain number of years.

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THE TREATMENT OF HEMATEMESIS AND MELENA BY A CONTINUOUS ALUMINUM HYDROXIDE DRIP.

A REPORT OF 21 CASES.

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THE acute emergency of hematemesis presents a troublesome therapeutic problem to the physician and potentially serious danger to the life of the patient. Except when the bleeding is slight, hematemesis usually is caused by the opening of an artery or vein. Since the immediate aim of treatment is to stop the bleeding, the procedure is commonly the same, whatever the primary cause of the hemorrhage. In most instances, the bleeding ceases spontaneously, no matter what the treatment, even on bed rest alone, but a certain number of patients with this type of hemorrhage die. Various procedures have been advocated, with the hope of reducing the number in whom gastric hemorrhage results disastrously, but the mortality rate, even with modern methods of treatment is much higher than is realized generally.

The mortality rate has varied in different series of cases recently reported. Hinton[11] reported a fatal outcome in 20% of those patients with severe gross hemorrhage; Bulmer,[6] in 10.7%; Chiesman,[8] in 25%; Allen and Benedict,[2] in 14.5%; Aitken,[1] in 11%; Tidy,[16] in 19%; Davis and Nevin,[9] in 21%; and Burger and Hartfall,[7] in 22.6%.

These figures present a challenge to physicians to attempt to reduce the mortality in this type of case, which is, as Rivers and

Wilbur[14] have shown, preponderantly the result of a gastric or duodenal lesion. They found that 76.8% of patients with hematemesis have peptic ulcer, and 12.4% have carcinoma; the remaining 10% have some other cause to account for the bleeding.

Many physicians have been too ready to accept blood transfusion as the simple solution to the problem. Blood transfusion, even when repeated and with large quantities, is not the solution, though it may be accepted as a routine procedure. The aim of treatment must be to arrest the hemorrhage and to prevent its recurrence. Since more than three-fourths of such cases are caused by a peptic ulcer, it should be recognized that there is no better way to arrest the bleeding and prevent its recurrence than by promotion of the healing of the ulcer.

Various forms of treatment, aside from transfusion, have been used in hematemesis and melena and the statistics just cited show that they have not been spectacularly successful. Hemostatics were used by the older physicians without any convincing results. Epinephrin, which causes contraction of the blood vessels when applied locally, is of little value in controlling bleeding in the stomach because the drug is too greatly diluted by the gastric contents when taken by mouth. Intramuscular injections of whole blood, anticoagulants and snake venom, as well as other substances, have been advocated by various workers, but none of these remedies has proved generally efficacious. Gastric lavage, which has been practised sporadically for 20 years, is rarely needed. Either hot water or ice-cold water has been employed by some in washing the stomach. The protecting clot is likely to be dislodged by this method, and it takes a great deal of temerity to try it. Soper[15] used gastric siphonage with a Levin gastro-duodenal catheter which was introduced through the nose. The continual withdrawal of gastric secretion, especially in the emergency associated with gastric hemorrhage, is unphysiologic and contraindicated because the usual loss of chlorides in hemorrhage and emesis, added to the loss of chlorides during the period of siphonage, may be of serious import.

Surgery has had a steadily diminishing number of advocates. Bevan,[5] Balfour[4] and Lahey[12] all advise against immediate operation, but reserve intervention later for recurrent bleeding. Surgical intervention in gastric hemorrhage entails great risks. If the bleeding is caused by an acute peptic ulcer, operation is likely to be futile, because there is no external indication of the presence of an ulcer and the stomach must be opened to deal with the bleeding point. The search for this is so difficult that the ulcer often is not found. In such instances, the shock of the operation in addition to the prolonged hemorrhage is almost certain to result in the death of the patient. On the other hand, a chronic ulcer is easily found. However, even in the presence of a known chronic ulcer, operation is inadvisable, because the chronic ulcer may not be the source of the

hemorrhage. It is impossible to exclude in such cases a complicating acute ulcer which would probably never be found at operation. Exsanguinated patients, even when they receive blood transfusions at the time of operation, are poor surgical risks.

Recent evidence indicates that after hemorrhage from an ulcer, much acid still remains in the stomach, and if this is true, it should influence the treatment of acute bleeding. It is exceptional for a single hemorrhage from a peptic ulcer to lead to death. The striking fact about the fatal cases is that, in all of them, the hemorrhage continued or recurred in spite of medical treatment. The hemorrhage from a blood-vessel in the stomach ceases as suddenly as it begins, as soon as the vessel is plugged with fibrin. Destruction of this fibrin is the cause of recurrence of the bleeding. It seems reasonable to suspect that the acid gastric juice digests the plug of fibrin and thus opens the bleeding vessel anew.

In this connection it is interesting that Meulengracht[13] of Copenhagen recently has treated hematemesis and melena by administering food, and, in the series of cases he reported, the mortality was much less than in other recorded series of cases of profuse gastrointestinal bleeding. In a group of 251 cases of severe hematemesis and melena in which this method was used, there were only 3 deaths, a mortality rate of 1.5%. Meulengracht contrasted the results in this series with those in a similar group of patients, admitted to the hospital in Copenhagen, whose treatment included complete abstinence from food. In the latter group the mortality rate was 7.9%. This author reported that feeding the patient who has hematemesis not only improves his general condition, but that in addition, the bleeding ceases more promptly than when food is withheld.

Meulengracht himself offered no physiologic explanation for this, but others, especially Alvarez,[3] have commented that the success of his method probably results from the reduction of hyperacidity. Alvarez suggests that "while trying to avoid dislodging the clot by food or persistalsis, we have left the delicate fibrin at the mercy of strong, unbuffered gastric juice." He adds that "the fact that he (Meulengracht) has been so successful indicates that the danger of digesting the clot is greater than that of dislodging it mechanically."

If this be true, the treatment of hematemesis, then, should consist of a method which continuously protects the bleeding area from the corrosive action of the hydrochloric acid. In view of Meulengracht's results with feeding alone, it was felt that they might be improved still further by a method which would furnish continuous counteraction of acid activity and at the same time preclude the undesirable possibility, even though it be remote, of mechanical dislodgment of the clot. Since exceedingly satisfactory results have been obtained in a large series of cases of uncomplicated peptic ulcer with the continuous administration of colloidal aluminum hydroxide through an

indwelling nasal Levin tube, it was determined to try this method in the treatment of hematemesis.

The material used and the method of administration in cases of hematemesis are the same as those which have already been described for the continuous control of acidity in peptic ulcer.[17] Colloidal aluminum hydroxide is a creamy white, gelatinous substance, mildly astringent and non-irritating. It is amphoteric, and hence

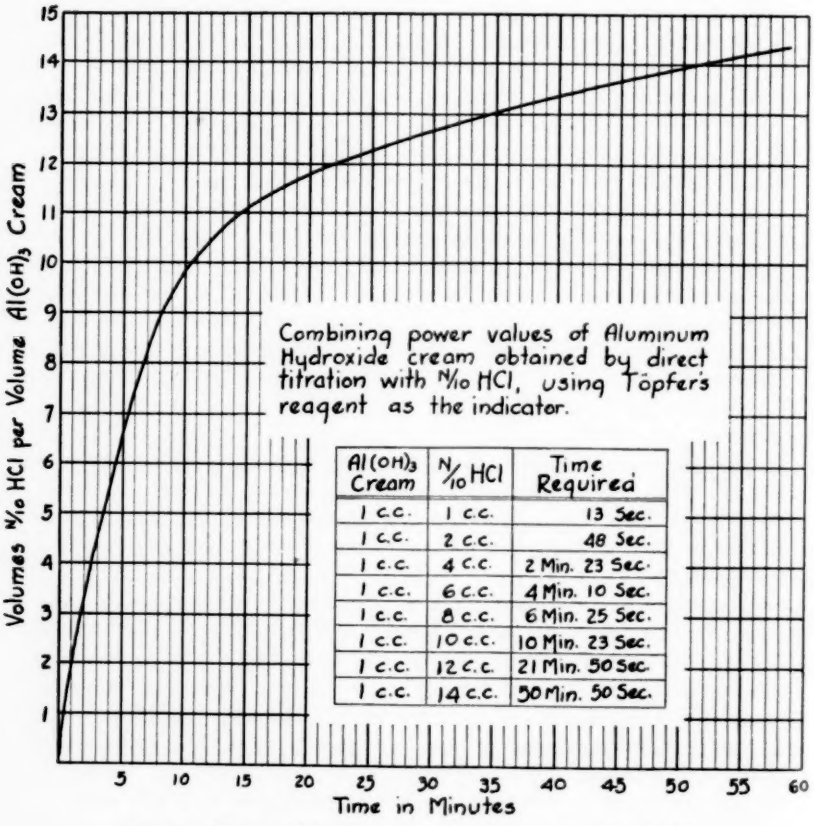
Volumes N/10 HCl per Volume Al(OH)3 Cream
Time in Minutes
Combining power values of Aluminum Hydroxide cream obtained by direct titration with N/10 HCl, using Töpfer's reagent as the indicator.
Al(OH)3 Cream | N/10 HCl | Time Required
1 c.c. | 1 c.c. | 13 Sec.
1 c.c. | 2 c.c. | 48 Sec.
1 c.c. | 4 c.c. | 2 Min. 23 Sec.
1 c.c. | 6 c.c. | 4 Min. 10 Sec.
1 c.c. | 8 c.c. | 6 Min. 25 Sec.
1 c.c. | 10 c.c. | 10 Min. 23 Sec.
1 c.c. | 12 c.c. | 21 Min. 50 Sec.
1 c.c. | 14 c.c. | 50 Min. 50 Sec.

FIG. 1.—The combining power of colloidal aluminum hydroxide.

its continuous administration presents no danger of alkalosis. The preparation contains 5 to 6% of aluminum hydroxide and about 0.6% of sodium chloride. Experiments *in vitro* demonstrate that this colloidal product, when undiluted, combines with twelve times its volume of tenth-normal hydrochloric acid within half an hour (Fig. 1). Large doses of colloidal aluminum hydroxide do not disturb the acid-base balance of the blood, as shown by estimations of

the blood chlorides and the carbon dioxide-combining power and the pH of the blood.[10] There is practically no absorption of aluminum from the gastro-intestinal tract. This substance, besides its exceptional antacid action, has the additional advantage that it protects the ulcer by coating it with a jelly-like mass, and by its astringent action assists in arresting the bleeding.

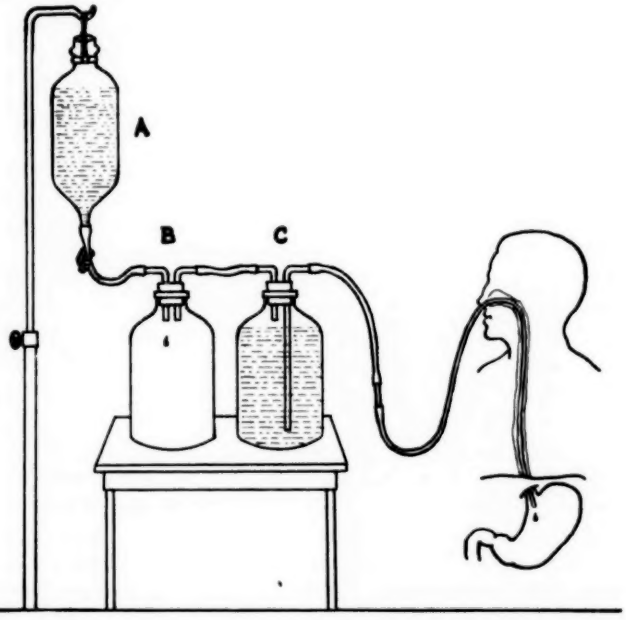

FIG. 2.—Flask A is filled with water, while clamp is closed. Bottle B is empty. Bottle C is filled with diluted (25%) colloidal aluminum hydroxide. The solution is allowed to siphon from Bottle C into a pan until it ceases. At this time there is a negative pressure created above the fluid level in Bottle C and also in Bottle B. The clamp beneath Flask A is adjusted so that the water will drip from Flask A into Bottle B at the rate of 10 drops a minute. Each drop creates an equivalent positive pressure in Bottle B and causes a drop to drip from the end of the Levin tube into the stomach. As the fluid level rises in Bottle B it causes the fluid level to fall correspondingly in Bottle C. The entire system must be air-tight at all times.

That it does actually prevent digestion of the fibrin clot has been shown experimentally. A clot of blood placed in a test tube filled with freshly aspirated gastric juice, and placed in an incubator at 37° C. shows evidence of digestion within 1 to 2 hours. However, when colloidal aluminum hydroxide is added to the tube containing the gastric juice and a small clot of blood, there is no evidence of digestion after 24 hours. Pepsin is not active in alkaline or neutral solutions. The optimum hydrogen-ion concentration for peptic digestion is between pH 2 and 3. When the pH of the solution is about 5, the power of pepsin to digest protein disappears.

A special apparatus for the continuous administration of colloidal

aluminum hydroxide had to be devised because this material is too thick, even in dilution, to flow through any tube constricted by a clamp to control the rate of flow. The apparatus consists of an elevated gravity flask filled with water, which is connected to an empty lower bottle by a rubber tube. The empty bottle is connected in turn to a siphon system which is filled with diluted colloidal aluminum hydroxide, and is connected to the indwelling nasal Levin tube. It is readily seen (Fig. 2) that the water inflow releases the siphon system outflow at precisely the same rate, that is, drop by drop. The system is automatic, simply requiring that it be kept air-tight and replenished with water and aluminum hydroxide solution each morning.

From September, 1935, to December, 1936, inclusive, 21 cases of hematemesis have been treated by this method in this hospital, with no deaths. This group includes only those patients who were admitted as emergency cases for the treatment of hematemesis as the leading often the only symptom. They vomited bright red or dark blood, or had tarry stools, in addition to secondary anemia sufficient to produce weakness, pallor, dyspnea or rapid pulse. Patients with blood-streaked or occasional "coffee-grounds" vomitus, occult blood in the stool or rare tarry stools were not included in this group.

In each case, as soon as the patient was admitted to the hospital, a Levin tube was passed through the nostril to the cardiac end of the stomach. This can be done without danger of injury to the bleeding area. The procedure will be effective even if the tube extends only to the lower end of the esophagus. If the tube reaches into the stomach, as shown by the withdrawal of gastric contents, it can be pulled up a few centimeters, so that the tip of the tube can not possibly cause any dislodgment of the clot or irritation of the bleeding point.

The proximal end of the Levin tube was connected to the drip apparatus which was regulated so that the colloidal aluminum hydroxide would flow into the stomach at the rate of 10 drops a minute. During the first 24 hours, the patient received 2 ounces of milk and cream every 2 hours. After that, the diet also included cooked cereals, gelatine, custards, cream soups, and rice and tapioca puddings.

Morphine was not used in this series of cases. Bulmer[6] and others have expressed doubts as to the wisdom of the present use of morphine in these cases on the basis that excessive immobilization of the stomach may be definitely undesirable. Rest was promoted in these patients by the administration of barbiturates and sedatives of similar type.

In every instance the hematemesis ceased promptly, and there was no recurrence of the bleeding. The patients continued to receive the colloidal aluminum hydroxide by continuous drip both day and

night for 10 days. All of them left the hospital in good condition, and there has been no recurrence of hematemesis or melena in any case.

Although this series of cases of hematemesis is too small to justify any definite prediction as to the reduction of mortality in this condition, the results in each of 21 instances have been so satisfactory that the outlook seems definitely more hopeful than by any method previously reported. The results in these 21 cases represent considerable improvement over those previously recorded at this hospital. From January, 1931, to September, 1935, there were 38 patients admitted with acute gastric hemorrhage (Table 1). Of these, 11 died. Of the 11 fatal cases, necropsy in 5 revealed 4 instances of duodenal ulcer and 1 of gastric ulcer. Operation in 3 other cases showed 1 gastric ulcer and 1 benign neurofibroma with ulceration, and in the third case, no lesion could be demonstrated. In the remaining 3 cases, a duodenal ulcer had been demonstrated in the roentgenogram.

TABLE 1.—MORTALITY RATE FROM HEMATEMESIS AND MELENA (ST. LUKE'S HOSPITAL).

Year.	Cases.	Deaths.
1931	8	3
1932	11	2
1933	7	2
1934	6	3
1935 (January–August)	6	1
COLLOIDAL ALUMINUM HYDROXIDE DRIP INSTITUTED.		
1935 (September–December) and 1936	21	0

Since September, 1935, when the new treatment was instituted, there have been no deaths in 21 consecutive cases. Of this group, 15 had duodenal ulcer and 4 had gastric ulcer according to roentgenographic evidence. Two patients related a history typical of ulcer, but no lesion could be demonstrated in the roentgenogram.

It would seem that the continuous administration of colloidal aluminum hydroxide presents certain advantages over mere feeding of the patient with acute bleeding. Since the object in both types of treatment is to remove the excess acid in the stomach which is likely to destroy the fibrin plug in the bleeding vessel, it seems logical to suppose that a method which furnishes continuous antacid action by means of a powerful agent would be preferable to one which is able to neutralize lesser quantities of acid and that only intermittently, and which also presents some hazard of mechanical dislodgment of the clot.

Summary.—After treating a large series of patients with uncomplicated peptic ulcer by the continuous administration of colloidal aluminum hydroxide by means of a special drip apparatus, we tried the same method in 21 cases of severe gastro-duodenal hemorrhage, with complete recovery in every instance.

This method offers definite advantages over treating hematemesis by feeding, as advocated by Meulengracht who reported better results than in any recorded series of similar type and magnitude, because it goes a step further in furnishing continuous, rather than intermittent, decrease of acidity with a more powerful agent, and at the same time promotes the healing of the ulcer. That is, this treatment accomplishes a two-fold purpose; the arrest of bleeding and the protection of the ulcer to facilitate its healing.

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TUBERCLE BACILLI IN THE GASTRIC CONTENTS—AN IMPORTANT DIAGNOSTIC AND PROGNOSTIC FINDING.

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The now widely used tuberculin test combined with Roentgen ray study of the infected, by means of the fluoroscope and roentgenogram, has made possible early discovery of pulmonary tuberculosis in the apparently healthy. These individuals usually will admit no symptoms. The physical examination of the chest frequently reveals nothing pertinent, and the temperature and pulse are normal. The pulmonary lesion may however be pathologically active, therefore of potential danger and in need of treatment; or it may be healed and in this instance a period of enforced rest would mean only an unnecessary loss of the individual's time. The problem then of the early infiltration is to determine its status at once, *i. e.*, is it pathologically active or is it healed?

In the past, recourse has usually been made to serial Roentgen ray films. Waiting for the roentgenogram to show change is not without serious objections, for if progression must occur to determine activity at the cost of further lung destruction, valuable time has been lost by not having instituted treatment earlier, since

further extension necessitates a longer period of confinement. Extension furthermore makes the prognosis less favorable.

Fortunately at our command are certain laboratory procedures which make possible determination of the probable course of the pathologic process before the roentgenogram shows its spread or retrogression. These laboratory procedures are the blood sedimentation test; repeated study of the total and differential blood count; and the examination of the morning fasting gastric contents for tubercle bacilli. This report will concern itself with the study of gastric contents.

Methods. As part of the student health tuberculosis program, all students showing parenchymal pulmonary infiltration are requested to enter the University Infirmary for a 3-day period of observation and study. The temperature and pulse are recorded at 4-hour intervals. Total white and differential blood counts are done by a technician, especially trained in hematologic work; the blood sedimentation rate is determined. The morning fasting gastric contents are aspirated on 3 successive mornings. Usually from 10 to 15 cc. of gastric juice is obtainable. If nothing can be aspirated, 15 cc. of normal saline or water is placed in the stomach through the tube. After 15 minutes this fluid is again withdrawn. The stomach contents are sent to the laboratory where examinations are made by direct stained smears, cultures and guinea-pig inoculations.

In the laboratory the specimen is centrifuged for 1 hour at 2000 r.p.m. The supernatant fluid is poured off and smears are made directly from the sediment and stained for acid-fast bacilli. The remainder of the sediment is thoroughly mixed with an equal quantity of 10% (by weight) sulphuric acid and allowed to stand for 45 minutes with occasional shaking. It is then neutralized with 8% potassium hydroxide using brom thymol blue as the indicator. After neutralization the specimen is again centrifuged, the supernatant fluid is poured away and the sediment is divided into two equal parts. One part is used for cultures and the other for guinea-pig inoculation. The cultures are made by inoculating each of 2 tubes of Holmes coagulated egg medium with 0.5 cc. of the sediment. The culture tubes are stoppered with corks and are incubated at 37° C. for 3 to 4 weeks. Occasionally positive cultures are obtained in a shorter time. The remaining half of the sediment is injected intraperitoneally into a guinea pig which is watched for a period of 6 weeks, at the end of which time it is killed and examined for gross evidence of tuberculosis. If gross lesions are found, the diagnosis of tuberculosis is confirmed by the presence of acid-fast bacilli in stained smears made either from an enlarged lymph node or the spleen.

To prevent the possibility of outside contamination, the Rehfuss tube, syringe, and bottle used in obtaining the specimen are all sterilized by boiling. The reagent solutions are prepared with sterile distilled water, and sterile pipettes are used. It is very improbable that tuberculous infection of guinea pigs occurs in the animal rooms: The laboratory uses a large number of pigs each year to test the sterility of vaccines and the virulence of diphtheria organisms. On no occasion has tuberculosis been found in these pigs. Many pigs are also used by the laboratory to determine the presence of tubercle bacilli in urine. In no instance has tuberculosis been found in the guinea pigs where tuberculosis of the genito-urinary tract was not present. The opinion is therefore held that contamination is not a factor in the high incidence of tubercle bacilli found in the cases presented.

It is planned to aspirate a group of normal patients' gastric contents, inoculate pigs, and note results.

Table 1.—Sputum and Gastric Content Study.

Case.	Date.	Lesion.	Sputum.	Gastric contents. Stain.	Culture.	Guinea pig.	Weight.*
	1935.						
1.							
87056	10–21	Mod. adv.	+	+	+	+	+10
Alb.							
2.							
84757	10–26	Miliary	–	–	–	–	+5
Silv.	10–27	tb. of	–	–	–	+	
	10–28	lungs	–	–	–	–	
3.							
88688	11– 2	Far adv.	–	–	C	–	+4
Ptson.	11– 3		–	–	–	+	
	11– 4		–	–	–	–	
4.							
87933	11–11	Minimal	–	–	C	–	0
Hott.	11–12	tb. pneu.	–	+	C	+	
	11–13		–	+			
5.							
77272	12– 9	Minimal	–	–	–	–	+7
St.	12–10		–	–	C	–	
	12–11		–	–	–	–	
6.							
76022	12–19	Minimal	–	–	–	–	+10
Stud.	12–20		–	–	C	–	
	12–21		–	–	C	–	
7.							
84566	12–28	Minimal	–	–	–	–	+4
Swen.	12– 9		–	–	–	+	
	12–30		–	–	–	–	
	1936.						
8.							
87362	1–25	Minimal	–	–	C	+	+10
Kalin.	1–26		–	–	C	+	
	1–27		–	–	+	+	
9.							
79975	2– 7	Minimal	–	..	..	..	–3
Grie.	2– 8		–	+	–	+	
	2– 9		–	+			
10.							
79831	3– 3	Mod. adv.	–	–	–	+	+18
Ann.	3 –4	1 bac.	–	+	–	+	
	3– 5	seen in 3 stains	–	–	–	+	
11.							
90446	3– 3	Minimal	–	–	–	–	+2
Seib.	3– 4		–	–	–	–	
	3– 5		–	–	–	–	
12.							
89205	3– 9	Minimal	–	–	–	+	0
Wrol.	3–10		–	–	+	+	
	3–11		–	–	+	Y	
13.							
32839	3–21	Minimal	–	–	C	+	0
Maish.	3–23		–	–	C	–	
	3–24		–	–	C	+	
14.							
88578	3–28	Minimal	–	–	–	–	–2
Homs.	3–29		–	–	–	–	
	3–30		–	–	–	–	
15.							
77106	4– 9	Minimal	–	–	C	+	+4
Lerq.	4–10		–	–	C	+	
	4–11		–	–	C	+	

Case.	Date.	Lesion.	Sputum.	Gastric contents. Stain.	Culture.	Guinea pig.	Weight.*
	1936.						
16.							
82513	4– 0	Minimal	–	–	–	–	+6
Goos.	4–21		–	–	–	–	
	3–22		–	–	–	–	
17.							
10001	4–23	Minimal	–	–	–	+	–12
Holm.	4–24		–	–	–	+	
	4–25		–	–	+	+	
18.							
83312	5–16	Minimal	–	+	+	+	+2
Eli.C.	5–17		–				
	5–18		–				
19.							
94089	10– 8	Mod. adv.	+	–	–	+	+8
M.Ett.	10– 9		+	–	–	+	
	10–10		+	+	C	+	
20.							
94490	10– 8	Minimal	–	–	–	+	+16
Ma. Tre.	10– 9		–	+	+	+	
	10–10		–	+	C	–	
21.							
94383	10–14	Minimal	–	–	C	+	0
R.Frie.	10–15		–	–	+	+	
	10–16		–	+	–	+	
22.							
94875	10–15	Minimal	–	–	–	–	0
N.Hard.	10–16		–	–	C	–	
	10–17		–	–	–	–	
23.							
92787	10–19	Minimal	–	+	+	+	–2
Spson.	10–20		–	–			
	10–21		–	–	–	+	
24.							
93491	10–19	Mod. adv.	+	+	C	+	–8
Sny.	10–20		–				
25.							
95181	10–26	Mod. adv.	–	–	–	–	–2
Sode.	10–27		–	–	–	+	
	10–28		–	–	–	+	
26.							
93631	10–26	Minimal	–	–	–	+	–1
Ander.	10–27		–	–	–	+	
	10–28		–	–	+	+	
27.							
92816	10–28	Mod. adv.	–	–	C	+	+4
Shil.	10–30		–	–	–	+	
	10–31		–	–	–	–	
28							
93257	11– 2	Minimal	–	–	–	–	+2
Suku.	11– 3		–	–	–	–	
	11– 4		–	–	–	+	
29.							
88261	12–15	Minimal	–	–	C	+	+6
Steff.	12–16		–	–	C	+	
	12–17		–	–	C	+	
30.							
95381	12–16	Mod. adv.	–	+	..	+	+9
Ega.	12–17		–	+	..	+	
	12–18		–	+	..	+	

C = Contaminated. Total positive 3 10 9 24 x

* Weight change during year—x–18 gained 127 lbs., 7 lost 30 lbs., 5 no change. Y– Pig died.

Results. In Table 1 the 30 cases presented have shown Roentgen ray changes subsequent to animal inoculation thus indicating pathologic activity. All except Case 4 regarded themselves as well. This individual had a bizarre type of slowly resolving pneumonia, the etiology of which was finally determined by finding tubercle bacilli in the gastric contents. His subsequent course substantiated the diagnosis of tuberculous pneumonia. Of especial interest is Case 2 who had miliary tuberculosis of the lungs, bilateral tuberculous epididymitis, and tuberculosis of the prostate and right testis. On no occasions were there constitutional symptoms. Treatment consisted of a bilateral epididymectomy, unilateral orchectomy and sanatorium care. It will be noted that in Case 10 though only 1 acid-fast bacillus was seen by stain in 3 specimens, all 3 pigs showed tuberculosis following inoculation. It will be noted that only 7 of the 30 cases lost weight, while 18 showed a gain.

TABLE 2.—EXAMINATION FOR TUBERCLE BACILLI, SPUTUM VS. GASTRIC CONTENTS.

Lesion.	Sputum +.		Gastric contents.					
			Stain +.		Culture +.		Pig +.	
	No.	%	No.	%	No.	%	No.	%
Minimal (21)	0	0	6	28.6	8	38.1	15	71.4
Moderately advanced (7)	3	42.9	5	71.4	1*	16.7	7	100.0
Far advanced (1)	0	0	0	0	0	0	1	100.0
Miliary (1)	0	0	0	0	0	0	1	100.0
Total + tbc. (30)	3	10.0	11	36.7	9†	31.0	24	80.0

* 1 of 6 cases.
† 9 of 29 cases.

In Table 2 the 30 cases are summarized. Only 3 (10%) were positive by sputum examination. Especially significant is the fact that though all the minimal cases (21) showed negative sputum examinations, 15 (71.4%) were positive by gastric aspiration and guinea-pig inoculations. That the absence of tubercle bacilli indicates a good prognosis is suggested by the course of the 6 minimal cases showing negative gastric studies. Five of these showed constant Roentgen ray retrogression from the time of their discovery. One showed slight progression before the institution of bed rest. Four have continued to attend the university and show clearing of the lesions. Three of these 4 have subminimal lesions. The fourth, though strongly advised to withdraw when first found to have minimal tuberculosis (maximum in amount), has shown marked retrogression of his infiltration.

It will be noted that by culture fewer cases were found positive than by stain. The explanation lies in the fact that cultures are very frequently contaminated by yeasts and spore-forming bacteria found so constantly in the gastric contents. Because of this, examination in the future will be limited to study of the stain and guinea pig.

Neglected has been the use of gastric content examination as an important aid in determining when treatment may safely be terminated. With Roentgen ray study many cases of pathologically active pulmonary tuberculosis are found in the minimal or moderately advanced stage without the occurrence of symptoms or fever. Commonly, treatment of such cases either at home or in a sanatorium is uneventful, and because of splendid progress, unwarranted permission to return to former activities is frequently given. In addition to repeated study of the total and differential blood counts, and the blood sedimentation rates, examination of the gastric contents may frequently reveal the persistence of tubercle bacilli. The necessity of further treatment is then obvious. On three occasions students have returned to school following months of treatment, with apparent improvement, but with bacilli still present in the gastric contents. In each case physical activity resulted in extension of the tuberculous process. It is only reasonable, therefore, to insist as further evidence to support the assumption that the lesion is inactive, that the gastric contents be free of tubercle bacilli on repeated examinations.

Summary. 1. The increasing use of the tuberculin test combined with Roentgen ray examination of the infected make manifest many cases of asymptomatic pulmonary tuberculosis.

2. Laboratory procedures frequently make possible determinations of the status of the lesion before the roentgenogram shows a change.

3. Tubercle bacilli were found in the gastric contents in 15 of 21 (71.4%) minimal cases of pulmonary tuberculosis in which the sputum was negative.

4. The absence of tubercle bacilli in the gastric contents suggests an inactive lesion, or if active that the prognosis is good. Retrogression occurred in 5 of the 6 cases in this series without the institution of treatment, other than increased hours of rest.

Conclusion. The examination of the gastric contents for tubercle bacilli frequently gives positive evidence (71% in this series) that the minimal infiltration is pathologically active and in need of treatment. The procedure is of inestimable value in helping to determine, especially in the asymptomatic cases, how long active treatment should be continued. One of the criteria of a healed lesion is the repeated absence of tubercle bacilli in the gastric contents as indicated by guinea-pig inoculation. Strict adherence to this principle would result in fewer recurrences in the many patients with apparent but not real cures.

I wish to express my thanks and my appreciation to the staff of the State Laboratory of Hygiene for their coöperation and assistance in carrying out this work.

PROTAMINE-INSULIN AND INFECTION.* †

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Infection is a potent factor in diminishing the efficacy of standard insulin, for in diabetes complicated by infection,[13] the dosage of insulin may be doubled or trebled, and yet fail to cause adequate combustion of carbohydrate. Similarly, in non-diabetics with infection, standard insulin, whether endogenous or injected, no longer exerts its usual effects on carbohydrate metabolism. The rôle of protamine-insulin in infection has not yet been studied, yet protamine-insulin, because of its prolonged action, will undoubtedly be widely used. It is therefore important to determine the effect of protamine-insulin during infection.

In an attempt to study its efficacy in the absence of diabetes, it was administered to 3 series of non-diabetic subjects, the first series consisting of 6 patients with tuberculosis, the second of 6 others with non-tuberculous infections, and the third of 4 individuals not suffering from infection. In general, the management of the patients began at about noon with dinner. Nothing further was ingested until 4 P.M.; when blood was drawn for glucose determination,[5] and protamine-insulin was then administered. At 4.30 the patient took supper and blood was collected at 8 P.M., midnight, and at 8 A.M. without any further ingestion of food.

In the first series of patients with tuberculous infection 4 had far-advanced pulmonary tuberculosis, a fifth, tuberculous peritonitis, and the sixth, a combination of both. The results presented in Table 1 were obtained from a small girl of 9 years with tuberculous peritonitis. She received 15 units of protamine-insulin, a large dose for her weight of 44 pounds. Despite the relatively great dose, the effect of insulin was capable of reducing her blood sugar only to 102 mg.%. Four of the remaining 5 patients of this series exhibited the phenomenon of insulin resistance. Table 1 also contains observations on one of the control patients with arteriosclerosis, but without infection. His blood sugar fell to 57 mg.% by 8 A.M. This result is typical of the 3 other controls.

* The results have been described in part in an address by H. E. Himwich before the Pediatric Section of the Medical Society of the County of Kings, New York, December, 1936.

† The insulin used in this work was generously supplied by the Eli Lilly Company, and contained added zinc. It might therefore, be called protamine-zinc-insulin.

TABLE 1.—PROTAMINE-INSULIN IN TUBERCULOUS PERITONITIS AND CONTROL.

	Diagnosis: 1. Arteriosclerosis. Weight: 150 lbs.	2. Tb. peritonitis. 44 lbs.	
Time.	Blood sugar, mg. %.	Blood sugar, mg. %.	Temp.
3:55 P.M.	96	119	98.8
4:00	—15 units protamine-insulin—		
4:30	—Supper—		
8:00	84	88	99.8
12:00	69	106	100.0
8:00 A.M.	57	102	98.6

Table 2 presents the observations on a little girl 2 years old, weighing 29 pounds, with acute tonsillitis. She is one of the second series of 6 patients with non-tuberculous infection, and received 4 units of protamine-insulin. Her blood sugar 18 hours later was 109 mg.%, and her temperature was high throughout the observations. However, a patient with carbuncle of the neck, and with no elevation of temperature, revealed a blood sugar of 101 mg.% 18 hours after the injection of 10 units of protamine-insulin (Table 2). Nevertheless, the other patients with insulin resistance that we observed did have fevers. Their respective diagnoses were malaria, localized peritonitis, mastitis and ureteral calculus.

TABLE 2.—PROTAMINE-INSULIN IN INFECTION.

	Diagnosis: 3. Ac. tonsillitis. Dosage: 4 units P.I. Weight: 29 lbs.		4. Carbuncle (neck). 10 units P.I. 120 lbs.	
Time.	Blood sugar, mg. %.	Temp.	Blood sugar, mg. %.	Temp.
3:55 P.M.	94	106.0	124	98.6
8:00	121	105.0	172	99.0
12:00	134	104.0	109	98.6
8:00 A.M.	109	99.0	101	98.2

In seeking controls without infection, a lad with a healing fracture of the tibia-fibula was examined who unexpectedly displayed insulin resistance. The observations were therefore to be repeated. The next day, however, he could no longer be called a normal control, for his temperature was 101°. Thus the insulin resistance of the previous day could be imputed to a developing infection.

The next experiment disclosed that hyperpyrexia, produced by diathermy, does not interfere with the hypoglycemic action of insulin. Standard insulin was used instead of protamine-insulin for two reasons: 1, protamine-insulin, as we have already shown, is not effective during infection, and 2, a more rapidly-acting insulin is required during the short 3-hour period of therapeutic diathermy. These results (Table 3) were obtained in an afebrile patient with chronic gonorrheal arthritis of the knee. The patient first had breakfast; hence the high initial blood sugar. Then he received 5 units of standard insulin before being subjected to diathermy for 3 hours. During this treatment, although his temperature was

raised to 104°, his blood sugar was reduced from 110 to 84 mg.%, a reduction which disappeared when the action of the standard insulin had ceased 3 hours later. The fall in blood sugar is significant, for diathermy of itself produces little, if any, change in blood sugar.[8] The result is similar to that of a control receiving the same dose of insulin, but not subjected to diathermy. From these observations we may conclude that infection, not fever, is the potent factor in the development of insulin resistance.

Previous experiments of Corkill[3] and other workers with standard insulin reveal that insulin resistance during infection is due largely to overactivity of the sympathetic nervous system and an excessive production of adrenalin. It remained to us to make similar studies with protamine-insulin.

TABLE 3.—DIATHERMY AND STANDARD INSULIN.

	Control.	5. Gon. arthritis patient.	
Time.	Blood sugar, mg. %.	Blood sugar, mg. %.	Temp.
7:40 A.M.		—Breakfast—	
8:00	97	110	99.2
8:05		—5 units standard insulin—	
11:30	81	84	104.0
1:30 P.M.	132	92	101.0

TABLE 4.—ADRENAL DENERVATION AND INSULIN RESISTANCE. AVERAGE VALUES. (CAT).

	Blood sugar, mg. %.		
Time, hrs.	Control.	Toxin.	Toxin denervation.
0	79	131	114
3	31	73	91
6	41	75	24
9	80	93	Died of hypoglycemia
30		248	

In these experiments insulin resistance was developed in cats by the injection of 5 minimum lethal dose of diphtheria toxin* 18 hours before they received one-quarter unit of protamine-insulin per kilo. To exclude excitement the cats were narcotized with nembutal while blood samples were drawn. In the first column of Table 4, headed by the word "Control," are the average values obtained from the 3 normal cats; in the second, marked "Toxin," are the average values of the 3 cats that had received diphtheria toxin. The post-absorptive blood sugar at the beginning of the experiment is higher in the cats that had received diphtheria toxin, indicating the antagonism towards endogenous insulin. Furthermore, after the injection of protamine-insulin the level of blood sugar does not

* To Dr. A. F. Coca, of the Lederle Laboratories, and to Dr. H. W. Lyall, of the New York State Hygienic Laboratories, our thanks are due for supplying the diphtheria toxin used in these experiments.

fall to as low as a value in the animals that received the toxin, while the premortal rise brings their blood sugar to the high level of 248 mg.%. Additional experiments, however, were necessary to test the idea that the insulin resistance was due to overactivity of the sympathetic nervous system. For this purpose 2 animals were given diphtheria toxin after they had fully recovered from an operation in which the right adrenal was removed and a splanchnectomy performed on the left side to cut off the adrenal medulla from nervous stimulation. Both these animals succumbed to hypoglycemia. In the last column, are the results of one of these cats which disclose the mortal fall of blood sugar. Such an observation, in which insulin resistance is eliminated with denervation of the adrenal gland, offers unequivocal support of the idea that the chief mechanism of the anatagonism is concerned with increased activity of the sympathetic nervous system, which favors glycogenolysis and thus raises the level of blood sugar.

TABLE 5.—ERGOTARTRATE AND INSULIN RESISTANCE. PROTAMINE-INSULIN ¼ UNIT PER KILO (DOG).

Time, hrs.	Blood sugar, mg. %.			
	Control.	Toxin.	Toxin.	Toxin ergotartrate.
0	102	88	87	100
1¼	...	..	..	91
2	...	..	..	64
6	70	96	86	
9	102	86	93	

Ergotartrate prevents sympathetic activity. Unlike splanchnectomy, this drug does not diminish the secretion of adrenalin; however, it interferes with the response to adrenalin after its liberation from the adrenal gland. A study of insulin resistance was therefore made on a dog injected with ergotartrate. Four results are found in Table 5: first, the control, the normal response to one-quarter unit of protamine-insulin per kilo body weight with sugar falling from 102 to 70 mg.% in 6 hours. In the second and third columns, marked "Toxin," the reactions of the animal after receiving diphtheria toxin reveal definite resistance to the action of insulin, for the blood sugar rises. That this resistance is due to overactivity of the sympathetic nerves was demonstrated by the injection of ergotartrate. When ergotartrate was injected in a dose of 1 mg., repeated in 1½ hours, the usual response to insulin returned (last column). Even in the profound toxemia of diphtheria, protamine-insulin regains its potency when the sympathetic response is inhibited.

Insulin resistance does not appear to be due to the presence of antibodies, for antitoxin creates no insulin resistance. In Table 6 are seen the effects of the injection of protamine-insulin in a depancreatized dog receiving 330 antitoxin units. Insulin successfully

lowers blood sugar from 282 mg.% to 148 mg.% in 6 hours, and to 129 mg.% in 8 hours. Similarly, an injection of completely neutralized toxin-antitoxin mixture in no way interferes with the action of insulin. These results emphasize that with the neutralization of the toxin, preventing the stimulation of the sympathetic nervous system, insulin sensitivity returns.

TABLE 6.—HYPOGLYCEMIC EFFECT OF PROTAMINE-INSULIN AFTER INJECTION OF ANTITOXIN IN DEPANCREATIZED DOG.
(5 units protamine-insulin.)

Time, hrs.	Blood sugar, mg. %.	Blood sugar, mg. %.
0	282	208
	Antitoxin	Toxin-antitoxin
6	148	122
8	129	100

Cannon[1] has advanced the conception that adrenalin and the sympathetic nervous system mobilize the resources of the body in an emergency. For the organism to increase the level of the blood sugar in a non-diabetic condition affords a readily available source of energy to the body. This mobilization of carbohydrate, however, occurring in response to the emergency of an infection developing during diabetes is no longer beneficial because it intensifies the diabetic condition. Thus this ordinarily defensive reflex mechanism, becomes injurious in the special condition of diabetes.

Adrenalin is not the only antagonist of insulin. The grave effects on the course of diabetes of an intercurrent hyperthyroidism are well known, and there is ample evidence indicating increased activity of the thyroid gland during infection.[9] The synergistic effects of the secretions of the thyroid and adrenal medulla are apparent in every case of hyperthyroidism which displays signs of hyperactivity of the sympathetic nervous system. Most important in this connection is the high level of blood sugar occurring so frequently in Graves' disease. In regard to effects on carbohydrate metabolism, thyroid therefore acts synergistically with adrenalin.

At least one other gland is important in the study of insulin resistance, namely, the anterior pituitary. As a result of the work of Houssay[6] and others, it is now held that the anterior pituitary gland contains a hormone which raises blood sugar. With increased secretion of the anterior pituitary gland insulin resistance should therefore develop. Whether one accepts the point of view of Corkill, Marks and White,[4] that the hormone of the anterior pituitary gland and adrenal medulla are synergistic in mobilizing liver glycogen, or that of Lucke, Heydemann and Hahndel[11] that the anterior pituitary functions *via* the adrenal medulla, it is apparent that both glands may act together to counteract the effect of insulin on blood sugar.

A review of the literature reveals that the diphtheria toxin exerts a direct necrobiotic effect on the islands of Langerhans[14] and the cells of the liver.[15] Moreover, the possibility exists that insulin is destroyed as a result of infection.[7] Nevertheless, the chief factor in insulin resistance is hormonal antagonism. This conception is presented in diagrammatic form (Fig. 1). Physiologically, the brain may send impulses by way of the splanchnic nerves to the adrenal medulla, there to excite the secretion of adrenalin which,

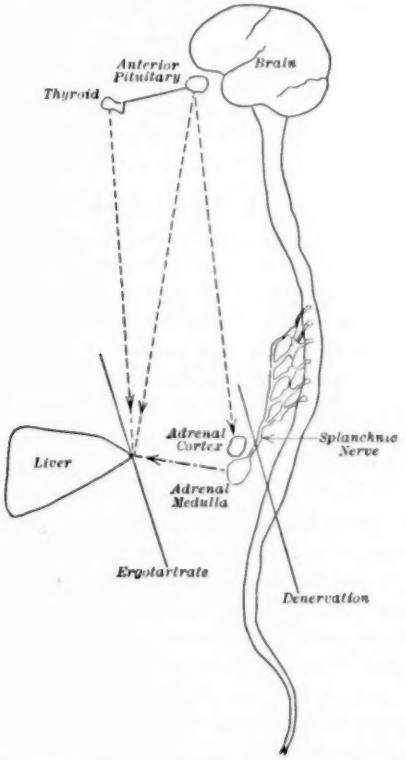

FIG. 1.—Hormonal antagonism to insulin.

in its turn, causes a breakdown of liver glycogen, and therefore an increase of blood sugar. The thyroid gland acts synergistically with the adrenal, as does the anterior pituitary, either directly or by way of the thyroid and adrenal cortex,[10] which may also influence carbohydrate metabolism. During infection the adrenal gland, the thyroid and anterior pituitary glands are all stimulated directly by the toxin. In a similar manner, as a result of the direct excitation by the toxin, cerebral activity may be increased and additional impulses sent to the adrenal gland by way of the splanchnic nerves

thus originating in the central nervous system a reflex resistance to the action of insulin.

Once set into operation it is difficult to inactivate the mechanism of insulin resistance. Ergotartrate is not advisedly employed. Although its successful therapeutic use has been reported, the dosage must be relatively large and therefore is not safe.[9] Denervation of the adrenal gland is not to be considered for several reasons which need not be discussed at this time. If signs of thyroid overactivity are present, the condition may be treated according to the accepted methods for the management of hyperthyroidism. It has been reported[12] that insulin resistance has been diminished by subjecting the anterior pituitary gland to radiation. However, this field is still largely experimental.

Since the hormonal response to infection cannot be controlled, it is preferable to go to the root of the trouble and combat the infection directly. In any case of insulin resistance a thorough search for the etiologic cause must be made in order to eradicate it. If this can be done surgically, there should be no procrastination. When surgical intervention is impossible or a general infection develops we have recourse only to increased insulin dosage, to be given more frequently.[2] Standard insulin may be preferable here because its more intense action is desirable in attempting to overcome insulin resistance. Furthermore, the administration of large doses of protamine-insulin is dangerous. Due to the prolonged activity of protamine-insulin it is possible that with improvement of the patient's condition a sudden decrease in insulin resistance may leave in the patient excessive amounts of active protamine-insulin.

Summary. Resistance is developed against protamine-insulin in non-diabetic patients with infection. The effect of the disease, in stimulating the endocrine glands and the nervous system, results in a rise in blood sugar, counteracting the effects of insulin whether endogenous or injected. It is suggested that standard insulin, with its more intense and rapid action, is preferable to protamine-insulin in cases of acute infection.

We are grateful to the Staffs of the Medical, Surgical, Tuberculosis, Pediatric and Pathologic Services of the Albany Hospital for assisting us wholeheartedly in this study.

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ARTERIAL HYPERTENSION.

THE SITE AND SIGNIFICANCE OF THE HIGH CHLORIDE CONTENT OF THE BLOOD.

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It has long been known that the chloride content of the blood of patients suffering from essential arterial hypertension is usually increased; but, so far as we are aware, the site of the increased chloride and its significance are unknown. Our work is an attempt to throw some light on these problems.

Methods. *A. Chloride and CO_2 Capacity of Plasma and Red Cells.* Blood was drawn from the median-basilic vein without stasis into a 30 cc. Record syringe containing sufficient potassium oxalate as anticoagulant, from 3 series of fasting individuals: (*a*) 103 young healthy subjects, including 5 women; (*b*) 13 elderly people with normal blood pressure, mostly women, as controls, and (*c*) 48 patients who, on repeated examinations had marked arterial hypertension, of whom 40 were women. All individuals with signs of renal disease, as indicated by albuminuria or MacLean's urea concentration test, were rejected. The elderly control group was included in order to determine whether the difference of age between groups (*a*) and (*c*) was a factor in the causation of their blood-chemistry differences.

The whole blood was then brought into equilibrium with alveolar air by the method described by Van Slyke.[11a] A portion was next transferred under oil, without loss of CO_2, to a centrifuge tube, centrifuged for 1½ hours and the plasma separated. The following were then determined:

1. The chloride content of both whole blood and plasma (methods of Myers and Short[8] and of Van Slyke[11b]).
2. The CO_2-combining power of both whole blood and plasma.[11a]
3. The relative volumes of corpuscles and plasma in the whole blood. (Hematocrit. Evans[4]).
4. The CO_2-combining capacity and chloride content per 100 cc. of red cells (by calculation from 1, 2, and 3).

When we had sufficient blood, all estimations were made in duplicate. This applies to the great majority of our figures.

Each red cell volume figure is the average of 4 determinations. We are aware of the difficulties in determining the true red cell volume% by any hematocrit method, as has been well shown by Ponder and Saslow.[9] Since however, their more accurate method requires 35 cc. of blood in addition to that required for chloride and CO_2 concentrations, it was obviously undesirable to use this method with human subjects. We were more concerned with showing comparative changes in the blood of each subject at various times, and as we used the same method for all (1600 revs. per min. for 1½ hours, in uniform bore hematocrit tubes) we feel, as indeed these authors state, that the hematocrit method is valuable for the determination of relative changes in cell volumes.

Another source of difficulty is the inaccuracy of many of the methods of chloride estimation in use. This has been well shown by Greenwald and Gross' comparison of methods.[5] We therefore used two methods, viz.: that of Myers and Short[8] and that of Van Slyke,[11b] in both our normal and hypertension groups, and, although the figures given by each differ, the differences brought out by each method between normal people and hypertension patients were found to be of the same kind (Fig. 1).

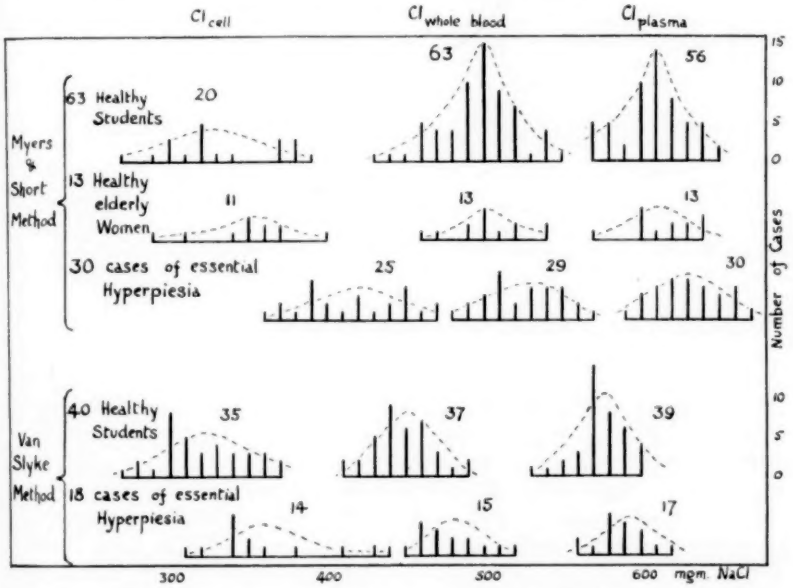

FIG. 1.—The distribution of chlorides in plasma $(Cl)_p$, whole blood, $(Cl)_{W.B.}$, and red cells, $(Cl)_c$, in people with normal and with high blood pressure. The abscissæ represent the numbers of individuals with the chloride concentrations indicated in the ordinates. The different results given by the two methods of chloride estimation, *viz.*, Myers and Short, and Van Slyke, are also shown. Note the marked rise in red cell chloride in high blood-pressure patients. The figures near each group indicate the number of individuals in that group.

Lest it be objected that the addition of oxalate to the blood might alter the distribution of ions between plasma and red cells, we would point out that Van Slyke[11a] has shown that, as regards the distribution of CO_2, practically no alteration takes place, whereas our own experiments showed that the addition of oxalate had no effect on the distribution of chloride (within 1%) compared with that in defibrinated blood.

B. Erythrocyte Volume-index and Blood pH. For this study we used a second group of patients, employing the microtechnique of Shock and Hastings,[10] but with the exception that, instead of using finger-prick blood and oxalate, we drew 3 cc. blood from the median-basilic vein without stasis into an oiled syringe, defibrinated with mercury (Eisenmann method[3]) and used the blood for hematocrit (3000 r.p.m. for 1 hour) and pH studies.

Blood counts were made by an experienced technician, the average of two counts checking within 0.5% being taken. After counts made on defibrinated blood and on a fraction of blood oxalated according to the method of Heller and Paul[7] were found to be identical on 10 occasions,

we confined ourselves to the latter method. From the above data the erythrocyte volume-index was calculated by the method of Haden.[6]

Results. Our results show: (Table 1).

TABLE 1.—AVERAGE BLOOD VALUES.

	Normal group.	Hypertension group.
Plasma Cl (as mg. NaCl)	581.0	588.0
Red cell Cl (as mg. NaCl)	328.0	373.0
Plasma CO_2 (as vol. %)	77.9	73.3
Red cell CO_2 (as vol. %)	54.0	51.5
Plasma total anions $(A)_p$ (as N solution)	0.1350 N	0.1332 N
Red cell total anions $(A)_c$	0.0805	0.0870
Ratio $\frac{(Cl)_c}{(Cl)_p}$	0.56	0.63
Ratio $\frac{(CO_2)_c}{(CO_2)_p}$	0.69	0.70
Ratio $\frac{(A)_c}{(A)_p}$	0.60	0.65
Red cell vol. %	49.0	46.7
Blood pH	7.34	7.34
Volume index (red cells)	1.015	1.008

1. The chloride content of the plasma in people with hypertension is practically the same as, or slightly higher than, that in normal people. In red cells, however, the chloride content per 100 cc. is raised considerably, on the average by 14% (Van Slyke's method) and 18% (Myers and Short's method). Fig. 1, however, shows that there is some overlapping of the normal and hypertension groups as regards red cell chloride, *i. e.*, people with high blood pressure do not necessarily have red cell chloride higher than may be found in normal people.

2. The CO_2 capacity of both plasma and red cells falls by a few volumes per cent, though again, as with the chlorides, the normal and hypertension groups overlap.

3. When the results above are calculated as the sum of the chloride and bicarbonate ions and plotted in terms of normality, the plasma values found for our group of normal young people is 0.1350 N (which is identical with that found by Atchley, Loeb, Benedict and Palmer[1]), while in our hypertension group the value is slightly less, 0.1332 N.

4. When from these results we calculate the ratio of chloride (or CO_2, or total anions) in the red cells to chloride (or CO_2 or total anions) in the plasma, we find that the ratios in the hypertension group are increased in value.

5. The average red cell volume per 100 cc. blood in our hypertension group was 46.7, a figure usually regarded as normal, though slightly less than that found in our normal student group.

6. There were no significant differences between the normal and hypertension groups as regards blood pH or erythrocyte volume-index. Thus in our normal group the pH and volume-index averages

were 7.34 and 1.015 respectively (with ranges of 7.29 to 7.39 and 0.917 to 1.057 respectively), while in the hypertension group the averages were for pH 7.34 and for volume-index 1.008 (with ranges of 7.28 to 7.50 and 0.849 to 1.160 respectively). (Table 1 and Fig. 2.)

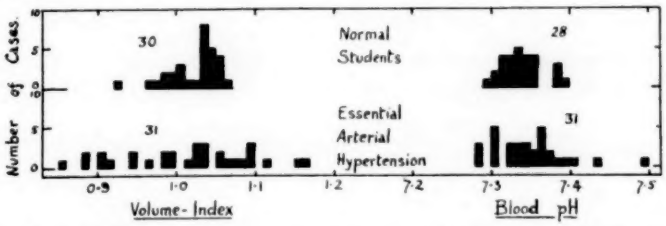

FIG. 2.—A comparison between two groups, (*a*) 30 normal students, and (*b*) 31 patients with arterial hypertension, as regards blood pH and volume index of red cells. Abscissæ represent numbers of individuals having the pH and volume index shown.

The Significance of These Results. The laws relating to the distribution of ions have recently been summarized by Van Slyke.[11c] One is to the effect that the ratio of chloride concentration in the cells to chloride concentration in plasma, is equal to the ratio of the bicarbonate concentration in the cells to the bicarbonate concentration in the plasma, which is in turn equal to the ratio of the concentration of anions in the cell to those in the plasma, and again to the ratio of the hydrogen-ion concentration in the plasma to the hydrogen-ion concentration in the cells. The numerical value of this ratio is determined by the concentration of base-binding hemoglobin in the cell.

This law may be expressed thus:

$$\frac{[Cl']c}{[Cl']p} = \frac{[HCO_3']c}{[HCO_3']p} = \frac{[A']c}{[A']p} = \frac{[H]p}{[H]c} = 1 - \frac{[Hb']c}{2[A']p} \quad \text{(Formula I)}$$

(The use of the brackets is to indicate concentration of ions)

In actual practice, however, this law is not strictly true. It has been found for instance, in defibrinated horse's blood, on which these laws were first worked out, that actually

$$\frac{[Cl']c}{[Cl']p} = 0.81 \frac{[HCO_3']c}{[HCO_3]p}$$

Van Slyke and his colleagues have further shown that the values of the ratios in Formula I rise or fall with increasing or diminishing H-ion concentration of the blood. This at once suggested that the rise in the ratio $\frac{[Cl']c}{[Cl']p}$ in our hypertension group might be the result of acidemia. This suggestion is supported by the recently published work of Doles[2] who claims to have found an increase in the volume of the individual erythrocytes (Volume Index) in arterial hyper-

tension, an increase which he asserts is directly proportional to the systolic pressure. Now it is well known that increase of volume index can be brought about by raising the H-ion concentration of blood, when both water and chlorides pass from the plasma into the red cells (Hamburger's phenomenon). Against the acidemia theory, however, was the fact that the ratio $\frac{[HCO_3']c}{[HCO_3']p}$ was not increased in our hypertension group. Our later studies, showing no change in blood pH and volume index, finally disposed of the acidemia hypothesis.

There are, however, other suggestions which have been put forward to explain the high cell chloride in arterial hypertension. Some of these are now being investigated.

Summary. In a study to determine the site of increased blood chloride in patients with arterial hypertension, and if possible its significance, it was found:

1. The increased blood chloride is wholly confined to the red cells.
2. This increased cell chloride is not the result of acidemia, since pH and erythrocytic volume-index showed no significant deviations from the normal.

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ELECTROCARDIOGRAPHIC CHANGES OCCURRING AT DEATH.

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Comparatively few electrocardiographic studies of the dying human heart are recorded in the literature. In 1933, Hanson and co-workers[4] collected 70 cases in which such studies had been made,

and added 25 cases of their own, making a total of 95. No other important additions have been made since then.

Many of the previously reported cases do not contain sufficient detail because the observations were made for very short periods before death. Changes that might have occurred before or after clinical death were therefore missed.

This paper covers electrocardiographic changes occurring at death in a series of 20 cases, in 6 of whom autopsies had been obtained. In many cases tracings were started several hours before expected death and continued from time to time after clinical death occurred. Some had tracings from days or weeks before, for comparison.

The purpose of this report is to add to the data collected by previous writers on the nature and mode of cessation of cardiac activity. It contains certain facts which might be used in the meager beginnings so far made to solve the mystery of life and death.

Case Reports. Case 1.—J. H., female, aged 70, died May 31, 1933. The postmortem findings were pneumococcus meningitis, bilateral bronchopneumonia, and acute tracheobronchitis. The heart weighed 335 gm.; myocardium was brown in color; mitral and aortic valves were slightly thickened; and there was slight shortening of the chordæ tendineæ. The coronary arteries were patent throughout and showed some yellowish intimal patches. Microscopically, there was marked fibrosis of the myocardium.

The electrocardiogram (Fig. II-A) 2 days before death shows a rate of about 122, regular sinus rhythm. Conduction normal. There is left axis deviation. The *P* wave is notched in the first, and diphasic in the third lead. *Q–R–S* slightly slurred in the second and third leads. Twenty-five minutes before death (B) there is nodal rhythm, rate 80. The *Q–R–S* complex is of lower voltage, slurred, *S–T* segment rounded and *T* wave negative. Twenty minutes before death (C) the rate is about 60; *T* wave is diphasic. Fifteen minutes before death (D) the rate is about 58, *S* wave is larger, the *S–T* segment is rounded and depressed and the *T* wave is diphasic. Ten minutes before death (E), there is shortening and slurring of the *R* wave, disappearance of the *S* wave, a high *R–T* take-off with positive *T* wave. There appears to be a wave on the *R–T* segment which might be of auricular origin. Five minutes before death (F) diphasic waves appear at the rate of about 52 per minute, preceded by fine, almost isoelectric vibrations which might be a part of the *Q–R–S* complexes. Three minutes before death (G) ventricular fibrillation appears. Three minutes after clinical death (H) there is cardiac standstill, with an occasional monophasic impulse, which appeared for about 2 minutes.

Case 2.—R. G., female, aged 43, died January 27, 1936, of lobar pneumonia. On postmortem the heart was found to weigh 250 gm. There were no gross or microscopic abnormalities except for an occasional atherosclerotic plaque in the coronary arteries.

The electrocardiogram at 10.15 A.M., 4 hours before death (Fig. III-A) shows regular sinus rhythm with a rate varying between 117 and 153 per minute. The *R–T* segment in the first and second leads is slightly depressed and rounded and slightly elevated in the third lead. At 2.07 P.M., 2 minutes before death (B), the rate is 75 per minute. The *P* wave is of low voltage in the first lead, negative in the second, and diphasic in the third. The axis is rotated to the left and the *T* waves are of higher voltage. At 2.10

P.M. (C), 1 minute after clinical death, monophasic ventricular waves take the place of the normal complexes and this continued for about 2 minutes, when the heart stopped.

CASE 3.—M. G., female, aged 65, died January 10, 1936. The postmortem findings were cerebral hemorrhage, bronchopneumonia, diaphragmatic hernia, and general arteriosclerosis. The heart was grossly normal, but microscopically, the myocardial fibers showed marked fragmentation, many brown pigment granules deposited at the poles of the nuclei, marked atherosclerosis of the small coronary branches, with almost complete obliteration of some of the lumina.

An electrocardiogram (Fig. IX-A) obtained at 4.55 P.M., about 9 hours before death, shows regular sinus rhythm, left axis deviation and low voltage T waves in all leads. The Q–R–S complexes are notched in the second lead. At 11.30 P.M., 2 hours before death (B), Q–R–S is of slightly voltage. At 1.40 A.M. (C), 3 minutes after clinical death, and continuing for 10 minutes, an occasional auricular impulse is seen and the ventricular impulses appear independently, at a rate of about 45 per minute. They are of lower voltage and have high R–T segments.

CASE 4.—A. D., female, aged 60, died October 17, 1935. The postmortem findings were cerebral thrombosis, subarachnoid hemorrhage and generalized arteriosclerosis. The heart weighed 310 gm.; mitral, tricuspid and aortic valves were moderately thickened. At the origin of the left descending coronary artery there was marked sclerosis and calcification, the lumen was patent in the proximal 2 cm., but narrowed down to a mere slit lower down. The right branch was patent throughout and there were atheromatous patches present in the intima. The microscopic findings were marked sclerosis of the small coronary branches with fibrosis of the myocardium.

The electrocardiogram (Fig. X) for a period of 1 hour after clinical death showed an occasional interruption of cardiac standstill by a supraventricular impulse.

CASE 5.—D. S., male, aged 58, was admitted on several occasions because of hematemesis. He died December 20, 1935, after a massive hemorrhage. The postmortem findings were hepar lobatum, esophageal varices, splenomegaly with thrombosis of the splenic vein. The heart weighed 300 gm. The wall of the right ventricle was 0.5 cm. thick, left ventricle 1.5 cm. The mitral valve was moderately thickened; the aorta showed marked tree barking. Microscopically, there was diffuse fibrosis of the myocardium and some brown atrophy.

The electrocardiogram (Fig. XVI-A) obtained 35 minutes before death, with patient unconscious and pulse hardly perceptible, shows regular sinus rhythm, rate about 129. The conduction time is normal. Five minutes before death (B), the complexes are of lower voltage. After clinical death (C), marked sinus bradycardia is noted with an occasional auricular premature contraction. The rate is variable, being at times as low as 15 per minute. The P–R conduction time is shortened from the previous 0.14 seconds to 0.10 seconds. There is thickening and widening of the S wave.

CASE 6.—P. P., a female, aged 36, admitted January 24, 1936, and died within a few hours after admission. The postmortem findings were generalized arteriosclerosis, and massive cerebral hemorrhage. The heart weighed 450 gm., the apex was blunt. The auricles were thin-walled; valves normal; the right ventricle measured 0.5 cm. in thickness with flattening of the musculi carnæ; the left ventricle measured 2 cm. in thickness, the musculature being slightly flattened. The coronary arteries showed minimal atheromatosis. Microscopically, there was diffuse fibrosis of the myocardium with brown atrophy and some fragmentation.

An electrocardiogram (Fig. XVII) obtained 10 minutes before death

shows marked sinus bradycardia and arrhythmia, with a rate varying between 25 and 63. The *P–R* conduction time is 0.14 to 0.18 seconds and the *Q–R–S* interval time is 0.08 seconds. There is a tendency towards right axis deviation with diphasic *T* waves arising abruptly from the *Q–R–S* complexes.

TABLE 1.—SUMMARY OF THE OTHER 14 CASES.

Case.	Sex.	Age.	Diagnosis.	Progressive electrocardiographic changes.
7 (Fig. 1)	F	16	Acute peritonitis following operation for chronic appendicitis	(*A*) Right axis deviation, nodal rhythm; (*B*) frequent ectopic ventricular impulses; (*C*) only ectopic impulses seen, *T* waves of lower amplitude; (*D*) changing of impulse focus; triphasic *T* waves; cardiac standstill followed.
8 (Fig. 4)	M	59	Atrophic cirrhosis of liver	(*A*) Regular sinus rhythm, left axis deviation; (*B*) lower voltage complexes; (*C*) auricular activity disappears; (*D*) multi-foci ventricular complexes; transient ventricular fibrillation (*C*, *D*)
9 (Fig. 5)	M	19	Lobar pneumonia, Type II	(*A*) Regular sinus rhythm, rate 144; (*B*) complete *A–V* dissociation, supraventricular and ectopic ventricular complexes; (*C*) cardiac standstill for 30 seconds; (*D*) nodal premature contractions, occasional auricular and ventricular ectopic impulses; (*E*) cardiac standstill, occasional ectopic ventricular impulse.
10 (Fig. 6)	F	40	Metastatic malignancy with possible metastasis to heart	(*A*) Regular sinus rhythm, rate 156, *Q–R–S* low voltage, notched; (*B*) sinus arrhythmia, rate 57, changing *Q–R–S*; (*C*) occasional auricular impulse, supraventricular impulses, rate 33, higher voltage, rate 27; (*D*) low voltage complexes, slurred, no *P* waves.
11 (Fig. 7)	M	44	Postoperative thyroid crisis	Complete cardiac standstill, interrupted occasionally by multifocal ectopic ventricular impulses.
12 (Fig. 8)	M	59	Coronary thrombosis	(*A*) Transient ventricular fibrillation, cardiac standstill, ectopic supraventricular impulses, sinus rhythm, *R–T* segment elevated and notched; (*B*) prolonged cardiac standstill, ectopic impulses resembling ventricular fibrillation.
13 (Fig. 11)	M	65	Bleeding gastric ulcer	(*A*) Regular sinus rhythm, right axis deviation, low voltage *Q–R–S*; (*B*) axis shift to left, low *T* wave; (*C*) rate 41, *P–R* 0.4 seconds, left axis deviation, diphasic *T* wave, prolonged *S–T* segment.
14 (Fig. 12)	F	26	Ruptured ectopic pregnancy	(*A*) Pre-operatively-regular sinus rhythm; (*B*) *R* wave higher, slurred, *S–T* depressed; (*C*) *Q–R–S* higher, well developed *S* wave; (*D*) *S* wave notched; (*E*) complete *A–V* dissociation, auricular rate 50, ventricular 24-28; (*F*) sinus bradycardia, ventricular premature contractions; (*G*) coarse ventricular fibrillation, short periods ventricular standstill.

TABLE 1.—SUMMARY OF THE OTHER 14 CASES—*Continued.*

Case.	Sex.	Age.	Diagnosis.	Progressive electrocardiographic changes.
15 (Fig. 13)	F	39	Mitral lesion, transient auricular fibrillation. Cerebral embolus	(*A*) Auricular fibrillation, ventricular rate 180, right axis deviation; (*B*) ventricular rate 136–158, intraventricular conduction time prolonged to 0.13 seconds; (*C*) bizarre ventricular complexes, 50–70 per minute.
16 (Fig. 14)	M	60	Cerebral thrombosis; hypostatic pneumonia	(*A*) Regular sinus rhythm, *Q–R–S* low voltage, slurred, left axis deviation, *Q* III; (*B*) intraventricular conduction time 0.12 second; (*C*) sinus arrhythmia, *Q–R–S* increased in amplitude, *S* III
17 (Fig. 15)	F	69	Cerebral hemorrhage	(*A*) regular sinus rhythm, left bundle branch block; (*B*) complete *A–V* dissociation; (*C*) auricular activity has ceased; (*D*) cardiac standstill interrupted by ventricular prematurity, progressive changes in *T* wave; (*D* and *E*).
18 (Fig. 18)	M	23	Rheumatic, mitral, and aortic lesions; auricular fibrillation; decompensation	Complete cardiac standstill, interrupted by short periods of ventricular fibrillation.
19 (Fig. 19)	M	32	Rheumatic, mitral, and aortic lesions; auricular fibrillation, congestive failure	(*A*) Auricular fibrillation, ventricular rate 120; (*B*) rate 32, *Q–R–S* changed; (*C*) delayed intraventricular conduction time; (*D*) occasional bigeminal rhythm; (*E*, *F*) slowed ventricular rate; (*G*, *H*, *I*, *J*) progressive changes in the complexes; (*K*) cardiac standstill interrupted by premature contraction.
20 (Fig. 20)	M	38	Attacks of syncope, convulsions; diagnosis not established	Fine ventricular fibrillation, interrupted by periods of multifocal ventricular paroxysmal tachycardia.

SUMMARY OF THE ELECTROCARDIOGRAPHIC CHANGES. Due to the great variety and rapidly shifting nature of the electrocardiographic changes, only the gross findings may be summarized. In the early records, 8 cases presented sinus tachycardia and 2 auricular fibrillation. The latter existed for many days before and cannot be considered one of the changes occurring in the process of death. This corroborates the findings of Willius,[14] Hanson and his coworkers,[4] Kahn and Goldstein[8] and Robinson.[11] Carter[2] claims that this disturbance does occur as a death phenomenon, but does not give any case reports.

Progressive sinus slowing occurred in 8 cases. Sinoauricular standstill followed. Ectopic impulses assumed the leadership of cardiac activity in many cases. Six developed nodal rhythm, 3 a single-focus ectopic ventricular rhythm, and several, multifocal ventricular impulses. In all these, the impulses produced a ventricular bradycardia at the same time that the auricles were either at a standstill or showed only occasional activity. In 1 case, there was a return from nodal rhythm and bradycardia to sinus bradycardia

and back again. Two showed an occasional return of auricular activity. Two others developed changes in the configuration of the *P* wave, with its ultimate disappearance. Two cases developed partial, and 3 complete auriculoventricular block. In Hanson's series, 7 cases out of 25, and in Willius', 4 out of 6, showed auticuloventricular block in various degrees. Two developed marked sinus arrhythmia. There were no instances of auricular flutter, although Willius claims to have observed 1 case in his series. Eight showed

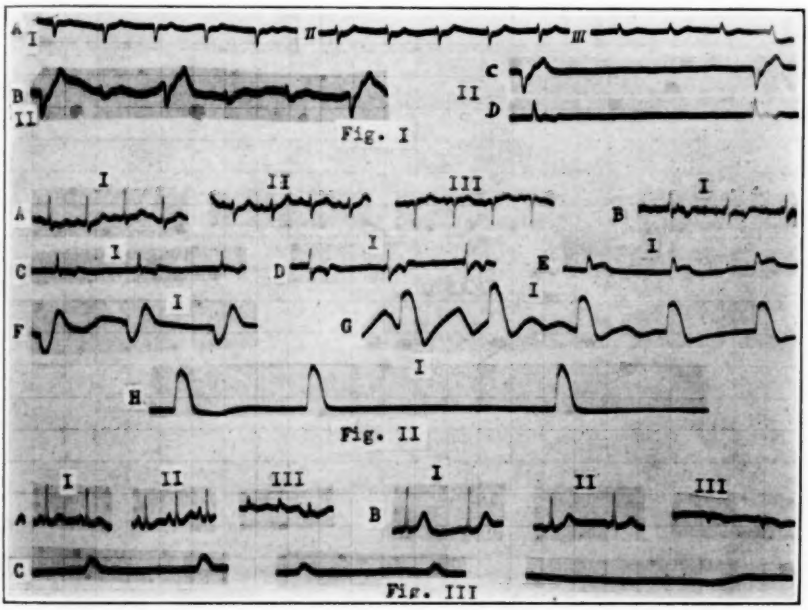

FIG. 1.—(Case 7.) *A*, three standard leads 10 minutes before death; *B* and *C*, the second lead 5 and 1 minute before death, respectively; *D*, immediately after clinical death.

FIG. 2.—*A*, 2 days before death; *B*, *C*, *D*, *E*, *F* and *G*, Lead I, 25, 20, 15, 10, 5 and 3 minutes before death, respectively; *H*, 3 minutes after clinical death.

FIG. 3.—*A*, 4 hours before; *B*, 3 minutes before and, *C*, 1 minute after clinical death.

complete cardiac standstill for variable periods, interrupted from time to time by ectopic ventricular impulses in 3, by ventricular fibrillation in 3, and by multifocal impulses with periods of ventricular paroxysmal tachycardia in 1 case.

Of intraventricular disturbances may be mentioned gradual changes in the *Q–R–S* complexes in 9 cases: diminished voltage in some, increased voltage in others, shifting of the electrical axis from right to left, shortening and marked widening with slurring and notching of the *S* wave or increased voltage of the *S* wave. Marked

progressive changes in the *R–T* and *S–T* components occurred in 6 cases. These consisted of rounding, depression, elevation, very high takeoff, prolongation, notching, shortening, widening and thickening. In 7 cases the *T* component also underwent definite changes, becoming isoelectric, diphasic, changing from a negative to a positive phase, increase in voltage, or taking an abrupt rise from the *Q–R–S* component.

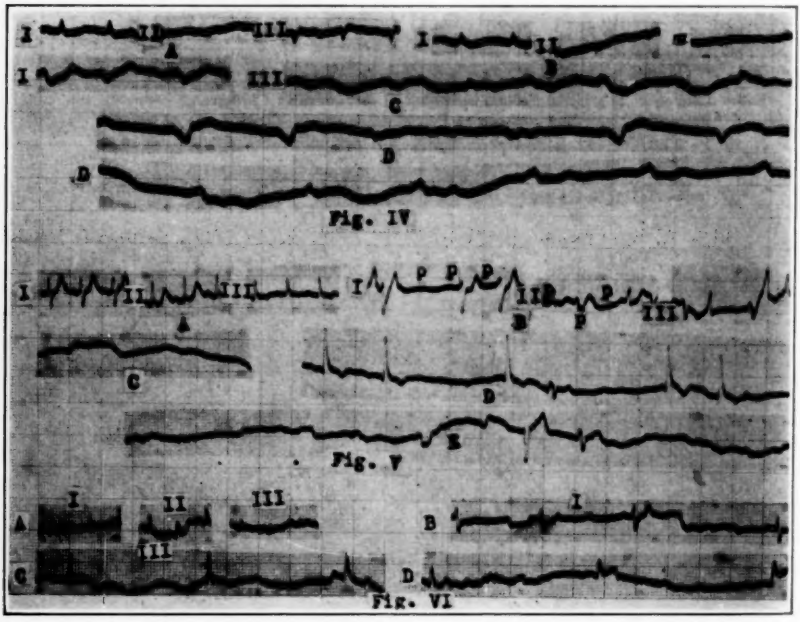

FIG. 4.—(Case 8.) *A*, three leads, 90 minutes before death; *B*, three leads, 40 minutes before death; *C*, Leads I and III, 5 minutes before death; *D*, Leads I and III, immediately after death.

FIG. 5.—(Case 9.) *A*, three leads, several hours before death; *B*, three leads, 15 minutes before death; *C*, cardiac standstill, lasting 30 seconds, 10 minutes before death; *D*, soon after standstill; *E*, after clinical death.

FIG. 6.—(Case 10.) *A*, *B* and *C*, 45, 15 and 5 minutes before death, respectively; *D*, after patient stopped breathing.

Four cases showed a rapid development of bundle branch block. In 7 cases, ventricular fibrillation occurred, either as a terminal event or for very short periods, interrupted by cardiac standstill or other disturbances. Hanson found this disturbance in 10 of 25, Willius in 4 of 6, and Kahn in 2 of 7 cases. In Turner's series[13] the incidence was 20% in 45 cases collected from the literature.

In several of our cases electrocardiographic changes occurred as long as 1 hour after clinical death. Similar observations were made by Turner,[13] Hoesslin,[7] Robinson,[11] Hasenfeld[5] and in experimental

animals by Bruns.[1] There were ectopic ventricular contractions, monophasic impulses, an occasional auricular or supraventricular impulse, bizarre complexes and sinus bradycardia. Ventricular fibrillation at times superseded the above.

Discussion. In times past there was a question of what part of the heart stops beating first at death. Koch[9] believed that the region of the coronary sinus, and Hering[6] that the sino-auricular node, was the last to die. G. C. Robinson showed that there was no constant area in the human heart that dies last.

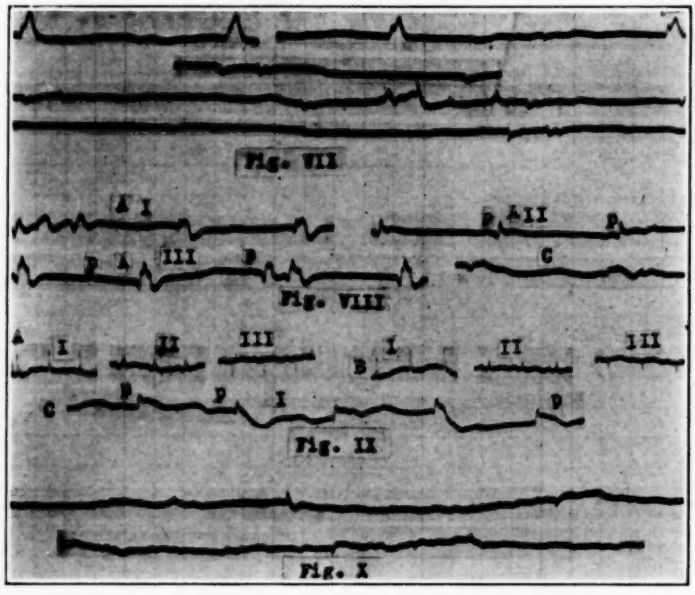

FIG. 7.—(Case 11.) Five to 15 minutes after clinical death.
FIG. 8.—(Case 12.) *A*, three leads, 2 minutes before death; *B*, Lead I, 10 minutes after death.
FIG. 9.—*A*, three leads, 9 hours before death; *B*, three leads, 2 hours before death; *C*, Lead I, 10 minutes after death.
FIG. 10.—One hour after death.

That contraction of the heart takes place concomitantly with electrical phenomena was established experimentally by Einthoven and Hugenholtz,[3] who contradicted the statement of Mines and Noyons[10] that electrical manifestations are recorded experimentally long after muscular contraction can be recorded. Einthoven and Hugenholtz showed this to be due to the use of an insensitive apparatus for registering mechanical beats.

Appreciation of this fact is valuable in interpreting the significance of the electrocardiographic manifestations before and after death. Hasenfeld's idea that electrocardiographic changes after clinical

death are caused by "possibility of hidden life" and that contraction of the heart is not the only cause of electrocardiographic phenomena requires elucidation and proof. There is one concrete factor besides contraction that may be associated with electrocardiographic manifestations, and that is "the current of injury." This factor might play some part in producing some of the bizarre, monophasic waves.

This study confirms the belief that death of the entire body or even special organs does not occur simultaneously. After clinical

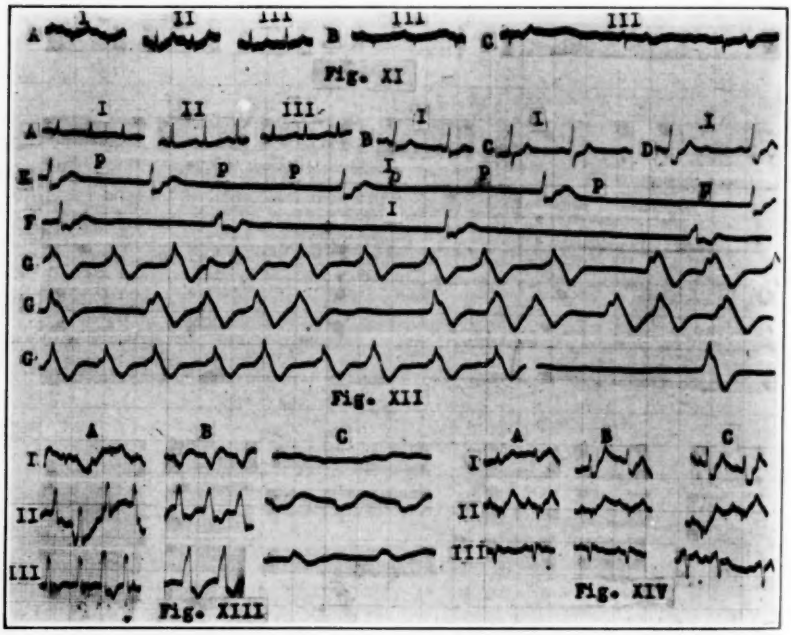

FIG. 11.—(Case 13.) *A*, three leads, 2 hours before death; *B*, Lead III, 45 minutes before death; *C*, Lead III, on death.

FIG. 12.—(Case 14.) *A*, three leads, 2 hours before death; *B*, *C*, *D*, *E*, *F* and *G*, Lead I, 30, 25, 20, 15, 5 and 2 minutes before death, respectively.

FIG. 13.—(Case 15.) *A*, three leads, 30 minutes before death; *B*, 5 minutes before death; *C*, on death.

FIG. 14.—(Case 16.) *A*, *B* and *C*, 1 hour, ½ hour and 2 minutes before death, respectively.

death, some organs or portions of organs continue to live. This was corroborated by Dr. Charles Norris who was quoted as having observed rare instances of auricular contraction 18 hours after accidental death, with the body kept on ice for that period.

There are many factors operative in bringing about the rapid alterations in the electromotive, and therefore contractile, forces and ultimate stoppage of the heart. Of these may be mentioned changes in the vagosympathetic control of the heart; anoxemia and

carbon dioxide accumulation in the body due to failure of the respiratory center; changes in the hydrogen-ion concentration of the blood; toxic factors; and nutritional disturbances. That anatomic disease of the heart itself is not the cause of the manifestations is evidenced from our observations that the electrocardiographic disturbances at death among those who showed conspicuous anatomic heart disease, postmortem or antemortem, were the same as in those who had anatomically normal hearts. Furthermore, there

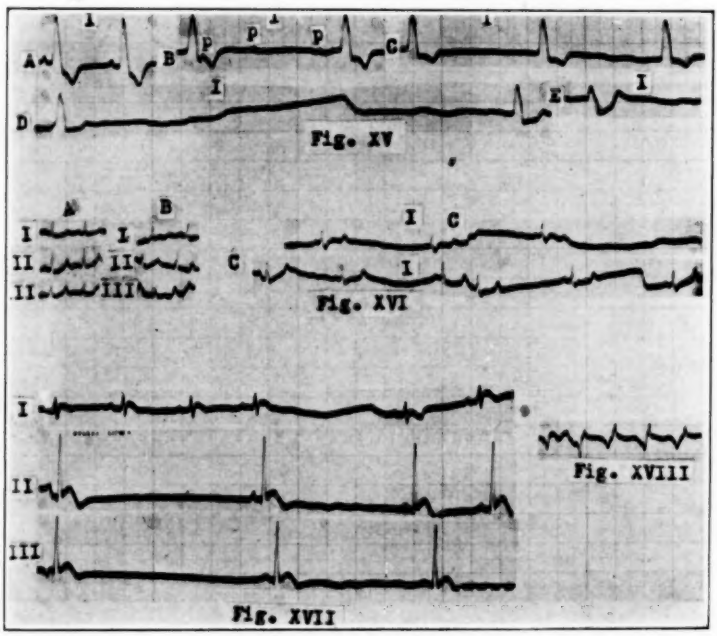

FIG. 15.—(Case 17.) Lead I. *A*, *B*, *C* and *D*, 15, 8, 4 and 2 minutes before death, respectively.

FIG. 16.—*A* and *B*, three leads, 35 and 5 minutes before death, respectively; *C*, Lead I, 10 minutes after death.

FIG. 17.—Three leads, 10 minutes before death.

FIG. 18.—(Case 18.) Small part of tracing 1 hour after death.

were no acute anatomic changes in the heart noted on postmortem examination that may be considered to have been produced immediately before death. The lesions found were of an older nature.

About half of our cases showed marked sinus acceleration of the heart early, due to excessive sympathetic nerve irritability. As time went on, sympathetic control was gradually lost and a vagotonic state developed, resulting in marked sinus slowing and final sino-auricular standstill in some, and auriculoventricular block in others. These manifestations were similar to those produced by the

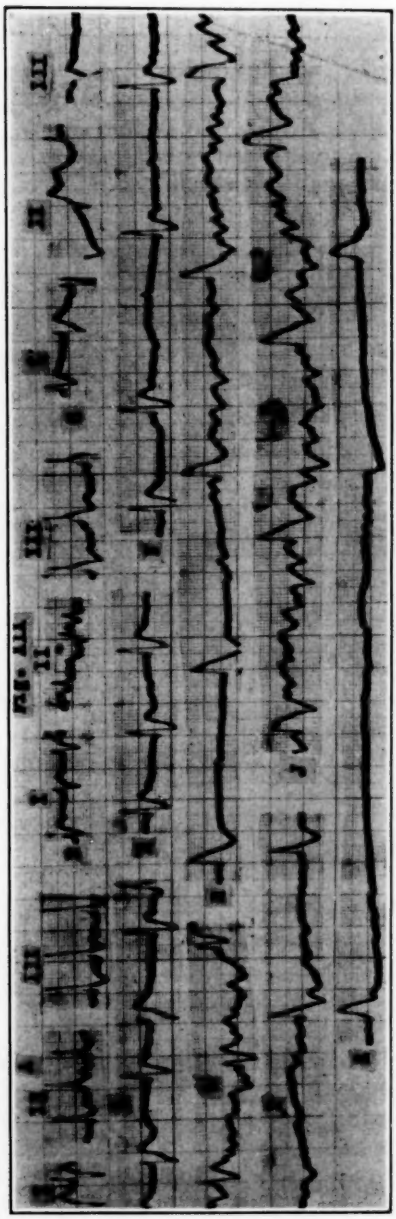

FIG. 19.—(Case 19.) *A*, *B* and *C*, three leads, 2 days, 5 hours and 2 hours before death, respectively; *D*, *E*, *F*, *G*, *H*, *I* and *J*, Lead I, 45, 40, 35, 30, 10, 5 and 3 minutes before death, respectively; *K*, Lead I, soon after death.

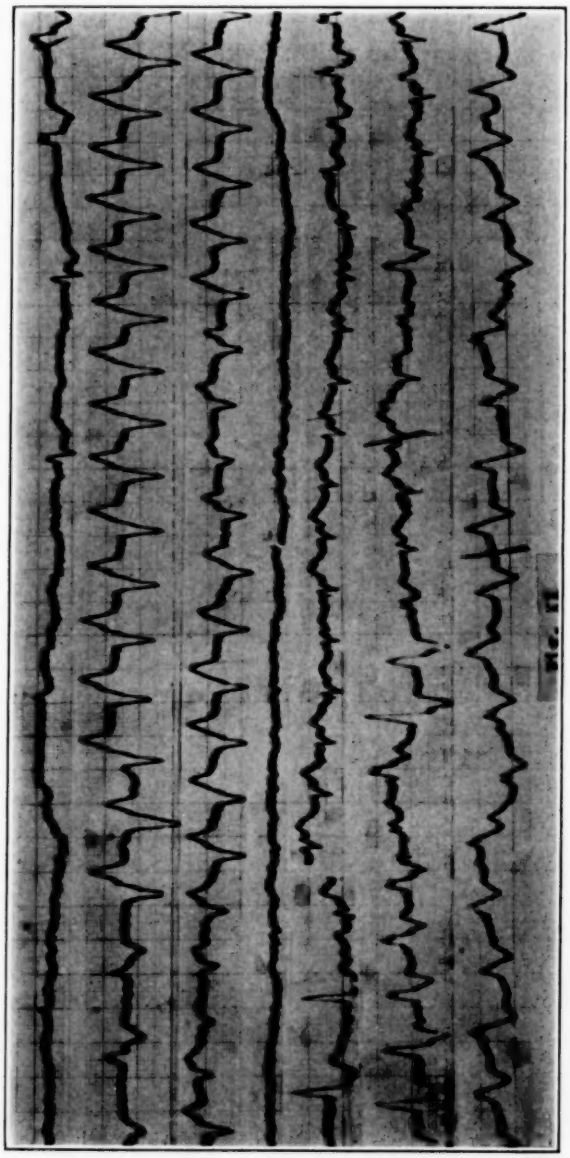

FIG. 20.—(Case 20.) Various phases observed within 1 hour before death.

carotid sinus reflex previously described by Sigler.[12] Marked sinus arrhythmia observed in 2 cases is further proof of vagotonia. The sinus slowing and standstill may partly be due to local anoxemia to which the sinoauricular node is particularly susceptible.

Marked vagal slowing or stoppage of the heart necessarily results in circulatory insufficiency and failure, aside from the vasomotor and respiratory failure present at these stages. Nutritional disturbances and anoxemia of the heart itself result in further changes in the electrical conductivity and mechanical contractility. This is shown in the changes of the initial as well as the terminal ventricular complexes from time to time. They depict gradual changes in the distribution of the excitation wave in the ventricular wall and the order of excitation and retraction. Transient focal blocking develops in various parts, increasing in degree to a point of bundle branch block. Local points of irritability in various areas in the ventricles and, at times, also in the auricles develop, resulting in aberrant impulses with uneven spread, either because of partial or total refractoriness in certain areas or focal changes in ionic composition and nutritional state of the muscle. Convulsive movements and localized tremors of the heart finally result, and are shown by ventricular fibrillation and other series of peculiar complexes.

Summary. Electrocardiographic studies were made on 20 cases before, during and after clinical death. The changes noted were: sinus tachycardia, followed by sinus bradycardia and sinoauricular standstill; development of ectopic foci of irritability, resulting in nodal rhythm, single- and multifocal ventricular premature contractions and ventricular paroxysmal tachycardia; appearance and disappearance of auricular activity; auriculoventricular block in various degrees; ventricular fibrillation; marked changes in the initial and terminal ventricular complexes; intraventricular conduction disturbances in various degrees up to bundle branch block. In many cases the electrocardiographic manifestations were noted as long as 1 hour after clinical death.

The factors responsible for these electrocardiographic changes appear to be disturbances in the vagosympathetic control of the heart, anoxemia, toxemia and local nutritional and ionic disturbances in the heart. That anatomic disease of the heart itself is not responsible for the ultimate manifestations is evidenced from the fact that these changes occurred in the normal as well as in the diseased hearts. The sinus slowing and standstill, as well as the various grades of auriculoventricular block, appear to be mainly of vagal origin. Intraventricular disturbances are dependent on the other factors. The latter disturbances depict changes in the distribution of the excitation waves and the order of excitation and retraction as well as transient focal blocking and localized partial or total refractoriness.

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SYPHILIS OF THE INTERVENTRICULAR SEPTUM AND VENTRICULAR TACHYCARDIA.

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The following concerns a case of proven syphilis of the interventricular septum with subsequent ventricular tachycardia, which is unique, as far as we know, in medical literature.

Case Report. A sailor, aged 35, was admitted to the British Hospital at Buenos Aires on April 13, 1936, under the medical care of Dr. G. Beyrne, in a state of weakness and general prostration which began suddenly 10 days before admission, while on board ship. On admission, he was complaining of vague pains in his chest and nausea followed by vomiting. The most important affliction he had had was rheumatic fever at 21, from which he recovered without involvement of the heart.

Physical examination showed his general condition to be satisfactory. Axillary temperature: 36.8° C., respiration, 24 per minute; pulse irregular, the rate ranging between 170 and 180 per minute. Blood pressure: 100/85 Hg mm. The apex beat was felt in the sixth intercostal space, in the midclavicular line. Both heart sounds were weak. There were no signs of congestive failure.

The intern diagnosed the case as paroxysmal tachycardia and prescribed intravenous digalena, digitalis per os, and in the evenings camphorated oil and sedol.

On the following day the patient's condition was the same, pulse rate being unchanged. Teleradiogram showed a much enlarged heart and congestion of the hilum of each lung. Electrocardiograms showed marked tachycardia of the ventricular rhythm. The curves are fairly typical of ventricular tachycardia (Fig. 1).

Two days later no improvement was noticed with digitalis and quinidine was given by mouth. On listening to the heart a peculiar "to and fro" murmur was heard at the apex. After that, signs of congestive failure developed as evidenced by congestion of both bases, tender and enlarged

liver, cyanosis and edema. White cell count was 23,000 per c.mm. The patient died suddenly during an attack of coughing and dyspnea on April 27, 1936.

Postmortem. Weight of heart 540 gm. Apex round in shape and formed by the left ventricle. Pericardium normal. Both coronary arteries (mouth, trunk and principal branches) were normal, except the left one which, in the zone of the interventricular septum, showed a series of whitish granulations following each other like beads of a rosary. The endocardium was normal. Auriculoventricular and pulmonary valves were normal. Aortic valves were slightly thickened. Myocardium was normal with the exception of the interventricular septum which, in the middle third sector, showed a whitish band stretching from one side of the septum to the other; it was distinct on the right side where it extended as far as the posterior wall of the right ventricle. In the aorta could be noticed small whitish slightly prominent zones vertically arranged and the size of a pin-head or larger.

The histologic examination of the zones in the septum showed a striking infiltration of mononuclears. Lymphocytes and plasma cells surrounded the vessels either irregularly or in masses (Hutinel's microscopic gumma); but sometimes they were not adjacent to vessels (Darier's miliary gumma). There was also granulation tissue in the form of neutrophil-fibroblast infiltration with abundant newly formed vessels (Fig. 2).

Endarteritis obliterans appeared in the small arteries and periendoneuritis was also observed in the nerves of that zone (Fig. 3). Some of the myocardial fibers were in fragments and some were compressed by granulation tissue. The right branch of His' bundle was destroyed completely by granulation tissue. A mild degree of white cell infiltration in certain zones was the only abnormality observed in the left branch which could be perfectly identified.

The ascending aorta showed cellular infiltration of the adventitia and endarteritis obliterans of the vasa vasorum, cellular proliferation of the elastic coat and parts of fatty degeneration in the internal coat.

Spirocheta pallida were occasionally observed (Dieterle Robert's silver impregnation technique) surrounding the lymphatic nodules, the septum and the vasa vasorum of the aorta (Fig. 4). They had 3 or 4 spirals, except one, which showed 7 spirals and was thickened and retracted with granular ends.

Discussion. Syphilitic lesions of the ascending aorta and mouths of the coronary arteries are common, but adult myocardial syphilis is exceptional and, according to Levine,[5] has little practical importance. Usually, myocardial syphilis is located in the upper zone of the interventricular septum where the auriculoventricular bundle is located; therefore it was assumed for a long time that complete heart block in the adult was usually caused by a luetic lesion in this area. This hypothesis has proved to be incorrect, the most frequent cause being sclerosis of the septum, coronary disturbance, and exceptionally lues (Gallavardin[4]).

Nowadays, certain conditions are required to prove that myocardial lesions are caused by syphilis. It is not enough to find a zone of sclerosis in the septum. The zone must have all the characteristics of a gumma or sclerogumma in which Schaudinn's spirochete must be found (Warthin[9]).

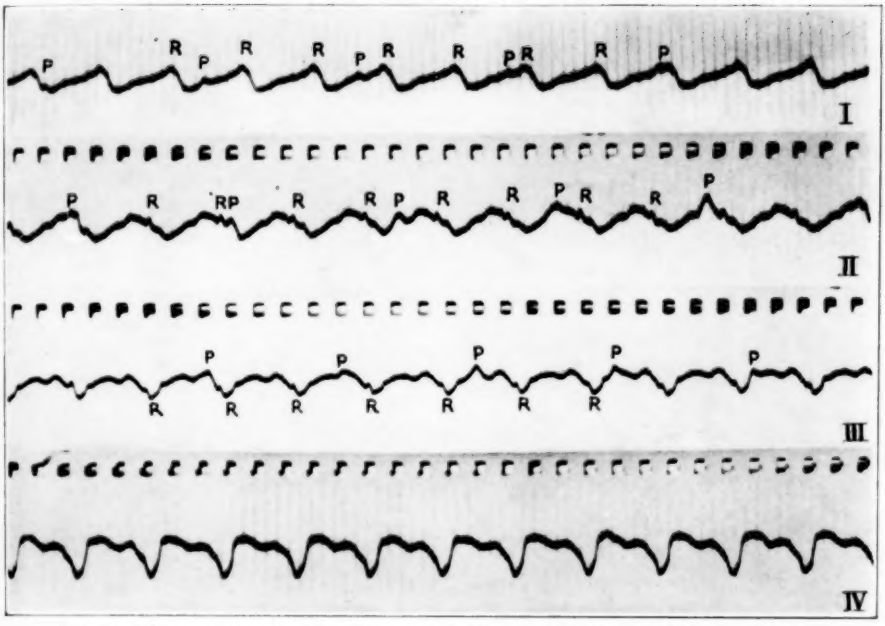

FIG. 1.—Electrocardiogram showing ventricular tachycardia resembling ventricular flutter in Leads I, II and III, but typical in Lead IV.

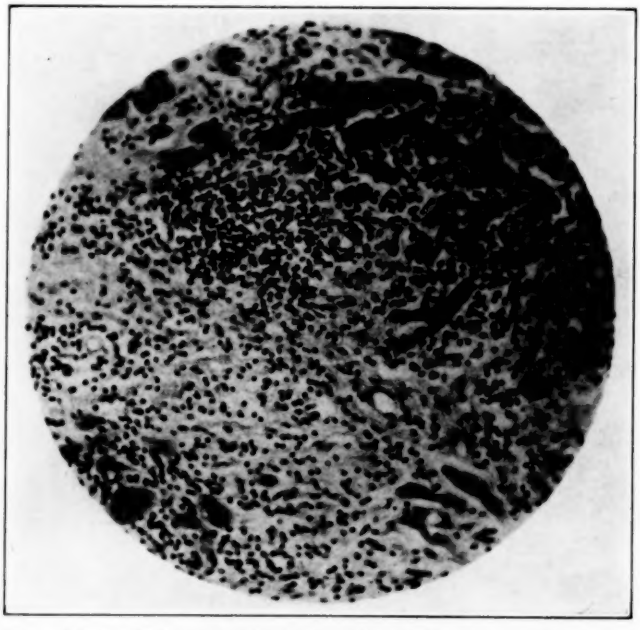

FIG. 2.—Myocardial mononuclear infiltration of the interventricular septum.

FIG. 3.—Endocoronaritis and perivascular infiltration. (Darier's microscopic gumma.)

FIG. 4.—Microscopic preparation of the interventricular septum showing one spirocheta with seven spirals (arrow).

Our observations fulfill these requirements, because there was a typical sclerogummatous lesion with a typical endocoronaritis and spirochetæ were found in the lesion. Most authors assume that syphilis of the interventricular septum gives rise to an auriculoventricular block; however, in our case there was an attack of ventricular tachycardia starting suddenly with nausea, vomiting, precordial aching, low blood pressure, leukocytosis and precordial frictions. These symptoms led us to the diagnosis of infarction of the interventricular septum when the patient was alive (Padilla and Cossio,[7] Cossio and Berconsky,[2] and Cossio.[1b])

Although the Wassermann test was positive, syphilis was not suspected as the cause, on account of the attack of ventricular tachycardia. Because most authors (Froment[3] and Mahaim[6]) do not mention syphilis as a cause of ventricular tachycardia, we thought that this case might have been a juvenile coronaritis (Pezzi[8]) of non-syphilitic origin.

According to our ideas (Cossio[1a]) and in view of the fact that the patient had a positive Wassermann test, we now believe he had syphilitic aortitis with an infarction of the septum caused by coronary thrombosis of syphilitic etiology.

Summary. 1. This report deals with a case of ventricular tachycardia caused by a syphilitic lesion of the interventricular septum.

2. It was a typical attack of ventricular tachycardia due to infarction of the interventricular septum.

3. The lesion was of the sclerogummatous type with endocoronaritis, and Treponema pallidum was found in it.

4. This observation, as far as we know, is the first of its kind in medical literature, and shows that a syphilitic lesion of the septum is able to produce an attack of ventricular tachycardia. In a case of prolonged attack of ventricular tachycardia, provided that the Wassermann and Kahn tests are positive, we must not only suspect infarction of the septum of the ordinary type, but also one of syphilitic etiology.

We are greatly indebted to Dr. G. Beyrne for allowing the publication of this case, and to Dr. S. A. Levine for his suggestions.

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MAINTENANCE OF THE FUNCTIONAL INTEGRITY OF OCCLUDED LARGE ARTERIES AS DEMONSTRATED BY THOROTRAST ARTERIOGRAPHY.

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In an article entitled "How Arteries Compensate for Occlusion," E. V. Allen[1] discussed various methods by which a collateral circulation may be established. His statements were the result of extensive experience with thorotrast arteriography, especially of the upper extremities. He noted how a collateral vessel may originate from a small artery above an occluded segment and pass down to empty into the same artery to maintain its integrity. He observed also how lateral branches from one artery may anastomose with an artery of similar size to compensate for occlusion. He indicated how the branches of one vessel could spread out to nourish the territory of neighboring occluded vessels; and he demonstrated the extensive network of very fine vessels which appears in the tissues when the main vessels are obliterated. Inasmuch, however, as Allen's illustrations all concern the arterial tree of the forearm and hand and comparatively small arteries, I should like to make some observations relative to the maintenance or reëstablishment of the fundamental integrity of large arteries of the lower extremity which have been occluded. This can perhaps best be done by describing 3 illustrative cases.

Incidentally, for the benefit of those unfamiliar with the subject or technique of arteriography, it may be mentioned that articles of Allen and Camp,[2] Veal and McFetridge[4] and Yater[3] may be referred to.

Case Reports. Case 1.—*Clinical History.* A. D., a white man, aged 50, suffered a serious compound fracture of both bones of the left leg in the middle of May, 1936. A cast was applied, but several days later a Steinman pin was inserted in order to secure better alignment of the fragments. General examination was negative, and urinalysis and Kahn test of the blood were essentially negative. The spinal fluid had been examined because of an acute psychosis, which was undoubtedly due to alcoholism; it was found to be normal. *Staph. albus* infection occurred in the wound of the leg. A hemogram revealed moderate anemia. For several weeks there was a daily elevation of temperature of 2° to 4° F. On July 10, 1936, he was discharged from the Gallinger Municipal Hospital in a light plaster cast.

While at home, on July 14, 1936, the patient suddenly developed an excruciating pain in the right thigh, "as if the muscles were being torn from the leg." This began at 9 P.M., about 5 minutes after he had had an alcohol rub. After about an hour the pain had traveled down to the leg and foot, where it persisted for 10 days and then slowly disappeared. At the onset the leg and foot were blanched except for a few bluish streaks

along the calf. After 3 or 4 days normal color gradually returned, but moderate swelling of the leg and foot developed.

On admission to the hospital on August 17, 1936, the right leg and foot were found to be still slightly painful and somewhat edematous. The color was almost normal, but the foot was a little cool and the pulsations were not palpable in its vessels. Arteriograms were made, and the patient was discharged in a few days.

The patient remained quite well and the fracture and wound of the left leg slowly healed. On September 3, 1936, he was carefully reëxamined. He stated that he had been in excellent health prior to his accident but had gained weight (up to 270 pounds) during the preceding 5 years and had had some dyspnea on exertion. Since April, 1936, he had taken digitalis intermittently. Physical examination did not reveal any arteriolar changes in the retinæ. The heart was apparently not enlarged and there were no murmurs. The cardiac rhythm was regular and the rate 100 per minute. The blood pressure was 190 systolic and 90 diastolic. The right foot blanched a little more than the left when it was elevated, but both feet retained fair color. Both feet became cyanotic when they were dependent. The legs and feet were slightly edematous and a little cool. Pulsations were not palpable in the feet.

Description of Arteriogram. An artist's exact pen and ink reproduction of the arteriogram made August 19, 1936, is shown in Fig. 1. The lower end of the femoral artery is missing for several centimeters, but its lumen is essentially normal in diameter above and below this area, which represents a completely occluded segment of the vessel. Just below this segment the wall of the vessel shows a slight indentation, which may indicate an arteriosclerotic plaque. Both above and below the occluded portion medium-sized branches of the artery are shown. Those above are mainly muscular branches, while those just below are anastomotic branches about the knee. One in particular is seen to pass downward in an undulatory course from the femoral artery just at its upper point of occlusion and undoubtedly empties directly into the upper portion of the popliteal artery, constituting a short detour of the current of blood around the obturated portion and thus maintaining the function of the main vessel below.

Case 2.—*Clinical History.* W. P., an old white man, aged 70, entered the Gallinger Municipal Hospital on August 20, 1936. Two weeks before a blister had appeared at the base of the right little toe; it was opened, and a few days later began to discharge pus. The foot became red and swollen. There had been no previous illness or symptoms referable to arteriosclerosis of any organ or extremity. Physical examination was essentially negative except for the extremities. The blood pressure was 176 systolic and 80 diastolic. The radial arteries were moderately hard. The left posterior tibial artery pulsated well, but the pulsation of the left dorsalis pedis artery was feeble. Neither the posterior tibial nor the dorsalis pedis could be felt to pulsate on the right. A round ulcer about 2 cm. in diameter was present on the lateral surface of the right foot at the base of the little toe. It was shallow and black and a small amount of pus was exuding. The right side of the foot was red and moderately swollen. The oral temperature was never above 99° F. Laboratory studies gave essentially normal results. Continuous hot magnesium sulphate soaks were instituted, and the patient was discharged as practically well on September 1, 1936. Arteriograms of the right lower extremity were made by the injection of 15 cc. of thorotrast.

Description of Arteriograms. Figure 2 is an exact drawing of the arteriogram of the right thigh. It shows absence of a shadow of the femoral artery above its lower half. The vessel below this point has a very irregular, "saw-tooth" lumen indicative of advanced arterio-

sclerosis. Undoubtedly there was complete occlusion of the femoral artery in most of its upper half, probably from just below the femoral triangle where the contrast medium was injected. A number of medium-sized arteries are seen descending from the upper portion of the thigh, branches no doubt of the femoral artery above the occluded portion. A tortuous one on the medial side of the femur is seen to empty directly into the femoral artery below the occluded portion.

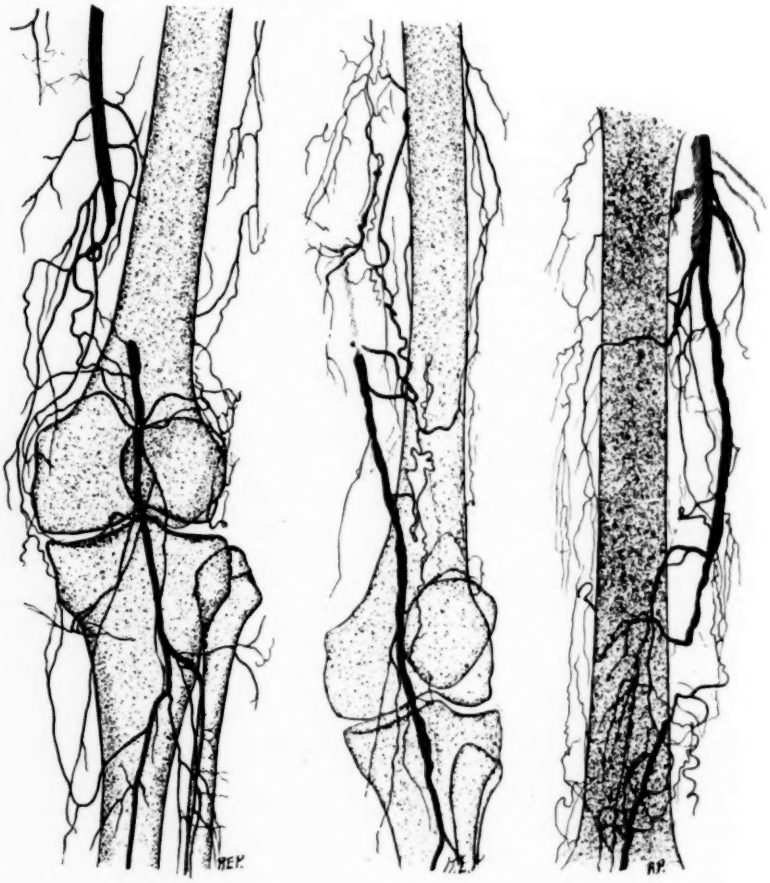

FIG. 1 FIG. 2 FIG. 3

FIG. 1.—(Case 1.) Exact drawing of arteriogram, showing evidence of complete occlusion in lower portion of femoral artery and collateral arteries connecting the lumen above and below.

FIG. 2.—(Case 2.) Exact drawing of arteriogram of thigh, showing evidence of occlusion of upper half of femoral artery and collateral arteries emptying into the arteriosclerotic femoral artery below.

FIG. 3.—(Case 3.) Exact drawing of arteriogram of thigh, showing markedly arteriosclerotic femoral artery with an area of occlusion in its lower third. Collateral arteries anastomose between the portions of the artery above and below this area.

The arteriogram of the leg showed absence of the shadow of the anterior tibial artery, which was probably completely occluded by atherosclerosis. However, many fine collateral arteries were demonstrated which probably assumed its function. The posterior tibial artery was seen to be occluded in its lower half but appeared again with a very narrowed lumen behind the internal malleolus. However, the occluded portion was bridged across by fine, long collateral vessels, which above were very undulatory.

Case 3.—*Clinical History.* F. C., a white man, aged 68, entered the Gallinger Municipal Hospital on January 14, 1937, complaining of loss of strength, some weakness of the left leg, moderate dyspnea on exertion, constipation and dysuria. He was found to have pernicious anemia, moderate essential hypertension, urethral strictures and prostatic hypertrophy. During the course of the physical examination the pulsations of the left popliteal artery were found to be feeble, and pulsations were not felt in the left posterior tibial and dorsalis pedis arteries. The right dorsalis pedis artery pulsated feebly, and the right posterior tibial artery did not pulsate. However, there were no color changes or trophic disturbances of either foot. The history did not reveal any suggestion of previous vascular trouble in the extremities. An arteriogram of the left thigh was made by means of 10 cc. of thorotrast, of which Fig. 3 is an exact line drawing.

Description of Arteriogram. The femoral artery has a very jagged border, due undoubtedly to arteriosclerotic changes. In the lower third of the arterial shadow there is a short gap, the result certainly of complete occlusion of the lumen. However, collateral arteries are numerous throughout the thigh; and a number of these arteries anastomose between the upper and lower segments of the femoral artery, allowing blood flow to continue through the main artery below the occluded portion.

Discussion. Arteriography is teaching us many things about the mechanics of the circulation in vascular disease which are not demonstrable otherwise. In Case 1 we see how Nature restored the function of a main artery by sidetracking the blood from above an occluded portion of the artery through a branch and bringing it back to the main trunk below. Undoubtedly other collateral arteries aided in this restoration. The history suggests embolism, but more probably sudden thrombosis occurred. The restorative alterations were made within a month of the time of occlusion.

Case 2 is quite different from Case 1. Here the occlusive process apparently developed very slowly, being due to gradual diminution of the lumen by atherosclerosis. But again we see the same detour of the blood through smaller arteries back to the main artery. Case 3 was similar to Case 2 in that the occlusive process was undoubtedly a very slow one due to atherosclerosis.

Readjustment of the circulation of the lower extremity by direct anastomosis allows one to make a better prognosis than in cases in which the main arteries are completely obliterated and in which the circulation is entirely dependent upon smaller vessels. In Cases 1 and 3 there was no gangrenous process, and in Case 2 trophic changes were minor and healed readily.

In cases of embolism in which recovery ensues it may be that the circulation in an extremity is reëstablished in the manner described,

at least at times. Arteriectomy as advocated by Leriche may be efficacious in that such a procedure conceivably may stimulate the development of direct anastomoses as well as the collateral circulation in general.

Only one illustration of a case similar to these could be found in the literature. This was Case 20 (p. 377) of Demel, Sgalitzer and Kollert.[3] It is probable, however, that such cases have been observed in large clinics where arteriography is frequently employed.

It is believed that most collateral vessels are merely enlarged and elongated branches that existed prior to the onset of vascular disease. Such cases as those described indicate that at times new anastomoses may develop, however, since it is quite improbable that a branch of an artery normally empties into the same artery a short distance below its origin.

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THE RESPIRATORY BASIS OF PERIODIC SUBCOSTAL PAIN IN CHILDREN.

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A "stitch in the side," first described by Pliny the Elder, is a frequent complaint of school children. As a harmless symptom it is often confused with gastro-intestinal, nervous or cardiac disturbances and occasionally as a rheumatic manifestation. The child in the midst of some effort gets a pain in the side, becomes pale and must rest for relief. If the pain does not pass immediately deep breathing, particularly exhalation, will alleviate the tense feeling. In every case the pain comes upon the child in motion, especially during quick jerks or jars of the body in the course of walking, running or some other activity involving effort. The site of the pain is usually below the costal margin, and contrary to other types of abdominal pain in children, subcostal pain is described and localized by them as a clear-cut experience.

Subcostal pain has been regarded as a transient circulatory disturbance in abdominal viscera by Mosler,[7] as a perisplenic phenomenon by Schmidt,[13] as a stigma of constitutional weakness by Benjamin,[3] as an index of sudden changes in the volume of the spleen by Bancroft,[2] as contraction of the spleen by Rautmann and Morse,[12] as a spasm of the intercostal muscles by Pembrey,[10] as

splenic tension by Mosse,[8] as irregular respiration by Herxheimer,[6] as reversed breathing by Nassau.[9] We sought the basis of this phenomenon in terms of the common findings characterizing the children complaining of periodic subcostal pain.

Required health examinations of 500 school children revealed 56 complaining of periodic subcostal pain on exertion. The complaint was usually volunteered by the child or parent rather than elicited by the physician. In each case, the nature, site and frequency of the subcostal pain were clearly represented during the examination. While other children were found on careful questioning to have similar experiences they were less well-defined and hence excluded from this study. The children with the periodic subcostal pain were therefore studied to determine the factor or factors common to this group.

RESULTS. 1. *Age and Sex of Group.* The children studied consisted of 24 boys and 32 girls, between the ages of 7 and 16 years. Whether the girls were more apprehensive about their person and hence more outspoken than the boys was difficult to determine, for sex did not appear to be a factor in the causation of subcostal pain. The distribution of age was as follows:

Age (years):	7	8	9	10	11	12	13	14	15
Boys	1	1	1	2	3	3	5	5	3
Girls	0	2	1	4	4	5	5	6	5

Increase in the frequency of subcostal pain with the onset of puberty exists despite the fact that the total number of children examined between 6 and 10 years of age exceeded those between 10 and 15. While the condition becomes manifest at 7, it is relatively infrequent until the beginning of the tenth year. The significance of age as a causative factor will become apparent from subsequent considerations.

2. *Site and Frequency of Pain.* Localization of the pain was clearly defined by all children studied. This was considered significant because in all other types of pain children usually point to the umbilical region as the area of involvement. This type of pain however was described clearly by each child, as a single site for most children and multiple in the remainder. Indeed the site, side and occasion of the pain were confirmed by repeated citations at subsequent examinations. Attempts to precipitate the pain in conformance with the description was difficult. Nevertheless, it was possible in several instances to initiate the experience by having the child twist his body with a quick jerk towards the side usually affected.

Twenty-six children experienced pain on the left side, 20 on the right and 10 on both sides. The distribution of the site of the pain was as follows: the spleen, 27 cases, liver 14, stomach 6, diaphragm 5

and heart 4. Most of the children experienced the pain on exertion, some daily but the majority about once or twice a week. Of the 56 children 3 occasionally felt the pain while resting in any position. In fact 1 of them sensed the pain by suggestion and had to double over to overcome it. All sorts of activities were considered responsible factors; 41 children complained of experiencing the pain during fast walking, 24 on running, 32 from athletic activities, 12 from dancing, 8 after meals.

3. *Body Build and Posture.* The linear type of body build was more common than the others complaining of subcostal pain. The distribution of body build was 21 cases of linear, 15 lateral, 15 medial and 5 muscular. The linear type children were hypertonic and all other types were hypersensitive emotionally. The striking feature common to all was poor postural alignment particularly of the kypholordotic type. In severe cases the flat chested child with a curved upper back, forward neck and shoulders showed some obstruction to breathing. The lower back compensates with a moderate to marked lordosis and a somewhat prominent abdomen.

4. *Breathing Patterns.* Every child susceptible to subcostal pain on exertion reported the prompt cessation of the pain with forced deep breathing particularly exhalation. With this as the acknowledged procedure for recovery we studied the relation of breathing to this phenomenon as the etiologic factor. The breathing space in the upper respiratory tract was inadequate in 26 of the children studied, the rest being normal. The distribution of children with obstructed breathing was as follows: chronic sinusitis, 12 cases, allergic rhinitis 10, enlarged adenoids 4.

The type of breathing of each child studied was determined from the recumbent resting position. The child was observed sideways for the silhouette view of the profile of the whole trunk in order to compare the degree of forward movement of the thorax and abdomen. Then the child was observed face to face to determine the relative parts played by the diaphragm and trunk muscles in both quiet and exaggerated breathing. Four types of breathing were noted in these children. First, thoracic, second abdominal, third simple thoracic-abdominal and fourth crossed thoracic abdominal. *Crossed thoracic-abdominal* type of breathing, first described by Czerny,[4] involves an oblique movement for each phase of breathing. The upward expansile inspiratory movement of the chest is so extensive that the increase in the size of the cavity is altogether too great for the lungs to fill. As a consequence the abdominal viscera, liver, stomach, and so on, are actually drawn upward into the chest by negative pressure instead of getting pushed downward and forward as in other types of breathing. The diaphragm is thus followed up into the chest cavity with a consequent depression instead of a protrusion at the pit of the stomach. The reverse of course main-

tains on expiration. Accordingly, the sinking of the thorax during expiration is accompanied by a forward thrust of the abdominal wall.

The distribution of the type of breathing was as follows: 29 showed crossed thoracic-abdominal type, 7 thoracic type and 5 simple thoracic-abdominal type. Although each type of breathing appeared natural for each type child, the respiration was far from effective during exertion. This was particularly evident with the 29 children who showed crossed type of thoracic-abdominal breathing. There was apparent limitation in the range of respiratory function; some could not execute a movement which would completely fill the lungs; some could not voluntarily use the costal and abdominal muscles separately; some could not relax the abdominal muscles during inspiration; some found it difficult to draw up the chest and expand the abdomen at the same time. With the group as a whole it became apparent that on the slightest additional demand the respiration became relatively insufficient.

We therefore determined the vital capacity of the lungs. Each child was requested to blow the largest possible breath into a wet-type spirometer. Several trials were allowed and the best figure that could be approximately repeated was taken as the proper value. The temperature of the water was maintained constant to prevent erroneous variations in volume. The number of readings for each child was too few to necessitate correction for practised performance. Since the conditions of each determination were individual, no one type of standardized procedure was followed. The measurement of vital capacity is a problem of understanding and coöperation by the child as well as one of lung capacity and chest flexibility.

The vital capacity values obtained were compared with the Baldwin standards of breathing capacity-height-age for both boys and girls,[1] and found to be consistently below the average norms. The number of children measured at each age group was too few to calculate the standard deviation or the coefficient of variation. The consistently low breathing capacity is significant because most of the children with subcostal pain were of the linear build which normally have a relatively higher vital capacity for height than do the lateral type of children. The children studied were obviously free from any pathologic conditions of either heart or lungs. The low normal levels of vital capacity in this group of children apparently related to their limited respiratory mechanisms.

5. *Therapy.* The respiratory deviations common to all children with subcostal pain were improved by specific therapeutic measures —clearance of obstructed breathing, correction of breathing patterns and postural defects. Paralleling the medical care of the upper respiratory tract some children were required to perform daily postural[11] and breathing exercises.[5] These were checked indi-

vidually in posture classes under the direction of a physiotherapist. Physical examinations were made at 2- or 3-week intervals and vital capacities were redetermined after the third month. Within this period the subcostal pain ceased to reappear even with strenuous effort. But there was a marked individual variation in the therapeutic response of each child. In 40 cases the vital capacity was

TABLE 1.—BREATHING CAPACITY DETERMINATIONS.

Boys.					Girls.				
Age, yrs.	Case.	Height, inches.	Vital capacity, cc.		Age, yrs.	Case.	Height, inches.	Vital capacity, cc.	
			Before.	After.				Before.	After.
8	M. B.	48.4	1340	1375	8	C. A.	45.5	1050	1150
9	K. G.	52.3	1610	1690		D. D.	48.8	1275	1300
10	W. C.	59.0	2175	2280	9	D. A.	53.7	1610	1690
	G. S.	55.5	1910	2020	10	F. B.	54.0	1640	1700
11	A. K.	60.8	2310	2500		J. G.	55.5	1785	1810
	J. J.	61.5	2495	2625		R. B.	57.0	1840	1920
	I. R.	56.5	2030	2175		S. T.	56.8	1910	1890
12	C. L.	62.0	2500	2610	11	B. S.	55.4	1740	1820
	E. M.	58.4	2180	2250		A. S.	56.0	1810	1860
	H. N.	60.1	2375	2450		E. T.	57.3	1850	1950
13	S. B.	61.5	2600	2725		N. S.	58.5	2055	2125
	R. O.	62.0	2650	2710	12	W. K.	58.0	2010	2075
	F. S.	63.8	2810	2925		P. Z.	59.5	2125	2250
	B. N.	64.5	2930	3050		D. F.	61.0	2280	2380
	T. V.	66.0	3050	3340		J. A.	61.2	2310	2390
14	K. H.	61.2	2680	2790		L. I.	62.8	2490	2610
	F. T.	63.5	2960	3070	13	E. J.	57.9	2010	2100
	A. G.	65.5	3200	3440		N. O.	59.1	2120	2250
	P. O.	68.0	3560	3550		I. H.	60.2	2250	2310
	R. C.	69.3	3550	3740		F. H.	61.8	2475	2525
15	A. S.	64.5	3260	3250		A. L.	63.1	2500	2610
	T. K.	69.5	3950	4160	14	M. J.	61.5	2480	2625
	J. R.	70.0	4060	4010		F. S.	63.2	2600	2690
						S. G.	63.9	2675	2755
						R. C.	64.6	2780	2900
						H. H.	65.7	2890	2925
						C. N.	66.1	2900	3010
					15	M. M.	61.9	2580	2610
						S. L.	63.6	2800	2850
						L. F.	64.6	2790	2910
						S. G.	66.1	2925	3050
						F. H.	66.2	2900	3090

markedly increased on assuming the corrected posture and improved breathing pattern; 14 cases were moderately altered; 8 developed a lowered breathing capacity which persisted in 2 cases. Improved vital capacity meant an increased latitude for diaphragmatic and thoracic excursion. Respiration was apparently facilitated and became deeper and somewhat slower.

Postural improvement was attained in terms of individualized criteria. With the marked individual variations in body build no one standard could be set up to define mechanically the best alignment for each child. Good posture was adjudged by the increase in the anteroposterior spinal curve, by the elevation of the chest in the position of almost full inspiration and by a firmness of the upper portion of the abdomen anteriorly. The habitual maintenance of such posture required many months because conditioned reflexes are acquired very slowly. Assiduous attempts at correcting faulty posture in 8 of the children studied put so great a task on the musculature of the thorax and abdomen that the vital capacity actually diminished. Indeed the subcostal pain previously experienced at infrequent intervals now became more frequent, particularly after the strenuous postural and breathing exercises. But with adjustment of the correction tasks to the children individually the stance improved and the subcostal pain cleared as with all the other children studied except in 2 cases.

Conclusions. 1. Required health examinations of 500 school children revealed 56 (24 boys and 32 girls) between the ages of 7 and 16 years, complaining of periodic subcostal pain on exertion.

2. Twenty-six children experienced pain on the left side, 20 on the right and 10 on both sides, the pain being referred to the spleen, liver, stomach, diaphragm and heart respectively. The pain occurred on exertion about once or twice a week during fast walking, running and participating in athletic activities or after meals.

3. Periodic subcostal pain occurred most frequently in the linear and medial types of body build with a kypholordotic postural defect. The pain was predominant in children with crossed thoracic-abdominal breathing and the abdominal type of breathing respectively, respiration proving ineffective on exertion.

4. Vital capacity determinations, obtained with a wet type spirometer and compared with the Baldwin standards of breathing capacity for height and age in boys and girls, were consistently below average norms.

5. Periodic subcostal pain ceased to recur in 48 out of 56 children after 3 months of daily postural and breathing exercises.

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THE ANEMIA OF MYXEDEMA: ITS CLASSIFICATION AND TREATMENT.

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It has long been known that a moderate degree of anemia is the usual accompaniment of myxedema.[4,9–11,18,28] However, in the clinical literature, one finds considerable disagreement, not only as to the type of anemia that is characteristic of myxedema, but also, as to its proper treatment. During the past 4 years, 20 cases of moderate to severe hypothyroidism have been studied in our hospital and out-patient departments. In each instance the metabolic rate was below −20%. The hypothyroidism was associated with an anemia in 9 instances (44%), of which 8 had adequate diagnostic and follow-up blood studies. In 2 of the patients, a diagnosis of both pernicious anemia and myxedema were made, and in a third case, the presence of pernicious anemia was questionable. These 3 cases will not be considered in this report. The remaining 5 served as a basis for attempting to correlate the clinical observations in the anemia of myxedema with our previous experimental findings.[23a,b]

Case Reports. Case 1.—Mrs. A. M., a 42-year-old white female entered our Outpatient Department, May 1, 1936. Her mother had died of pernicious anemia at the age of 58. In addition to the patient's typical symptoms and signs of myxedema that had been present for about 12 years, there was a well marked lemon-yellow pallor of the skin, a moderate papillary atrophy of the tongue, and bilateral sluggish deep and superficial reflexes. The vibratory sense was intact.

The blood count disclosed a hemoglobin of 69% (11.7 gm.), erythrocytes 3,860,000, and leukocytes 5700 with a normal differential count. The mean corpuscular volume was 87 cu. microns, the mean corpuscular hemoglobin 30.5 micromicrograms. The icterus index was normal; the reticulocytes 0.1%. A normal amount of free hydrochloric acid was present in the gastric content, and the stool was negative for blood. The basal metabolic rate was −43%.

Before thyroid extract was started, the patient was given 3 cc. of liver extract (Lederle), intramuscularly, on 3 successive days. During the following 10-day period, there was no increase of the reticulocytes. Thyroid extract, 4 grains daily, was then given followed by a prompt rise in the metabolism, but with no effect on the number of reticulocytes. Six weeks after taking thyroid extract, the hemoglobin was 64% (10.8 gm.), the erythrocytes slightly decreased to 3,300,000. The addition of iron and ammonium citrate, 90 grains a day, to the maintenance dose of thyroid extract, produced a slow but sustained increase in the hemoglobin to 87% (14.7 gm.), and in the erythrocytes to 5,330,000 (Fig. 1).

With improvement in the blood, the tongue and neurologic changes completely disappeared.

Case 2.—Mrs. L. C., a 30-year-old white female, entered this hospital, May 20, 1935, with a history of diabetes for 7 years. A year before admis-

sion, she had first noted a progressive weakness, lemon-yellow pallor, dyspnea and palpitation on exertion, and numbness and tingling of the extremities. The physical examination disclosed a rather obese, slightly icteric, pale individual with a dry scaly skin. The tongue was pale and smooth. All deep and superficial reflexes were sluggishly present, and the vibratory sense was absent below the knees.

The blood count showed a hemoglobin of 65% (11 gm.), erythrocytes 3,090,000, and leukocytes 4200 with a normal differential formula. The mean corpuscular volume was 93 cu. microns, and the mean corpuscular hemoglobin 32% micromicrograms. The icterus index was 25 units, the reticulocytes were 0.55%. The bleeding and clotting time were normal, as well as the fragility of the red blood cells. There was a persistent achlorhydria of the gastric content, even after histamine stimulation. There was very slight occult blood present in the stool. The hyperglycemia and glycosuria, a difficult problem, does not concern us in this report.

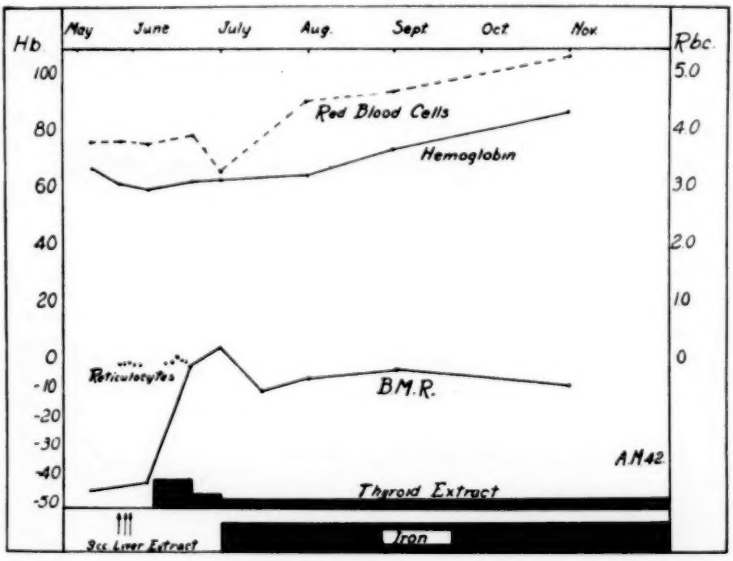

FIG. 1

A diagnosis of pernicious anemia was made, although her age and the absence of distinct macrocytosis was against it. Further doubt as to this diagnosis was expressed when, after receiving daily doses of intramuscular liver extract for 3 weeks, no effect on the reticulocytes had been noted. The daily administration of 90 grains of iron and ammonium citrate, first alone, and later in combination with oral and parenteral liver extract, failed to cause any significant change in the blood (Fig. 2*A*). It was not until Dr. Frank Conlin first saw the patient, 16 weeks after admission, that myxedema was recognized and a basal metabolic rate obtained and found to be −43%.

Though thyroid extract caused a prompt improvement in the patient's general condition, a temporary decrease of the blood counts was again noted during the first 2 months of treatment. During 7 months of thyroid therapy, without liver or iron, both the hemoglobin and the number of erythrocytes

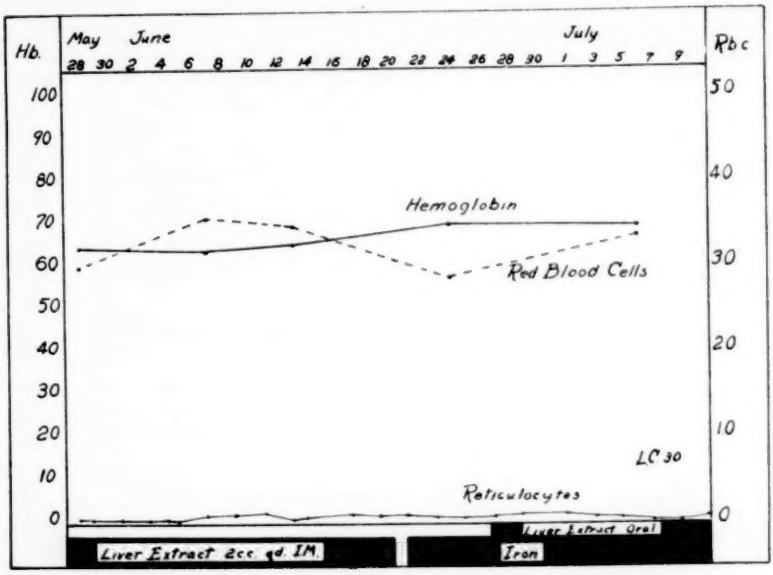
Hb.
May
June
July
28 30 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 1 3 5 7 9
Rbc
100
90
80
70
60
50
40
30
20
10
0
5.0
4.0
3.0
2.0
1.0
0
Hemoglobin
Red Blood Cells
LC 30
Reticulocytes
Liver Extract Oral
Liver Extract 2cc. q.d. IM.
Iron

FIG. 2 A

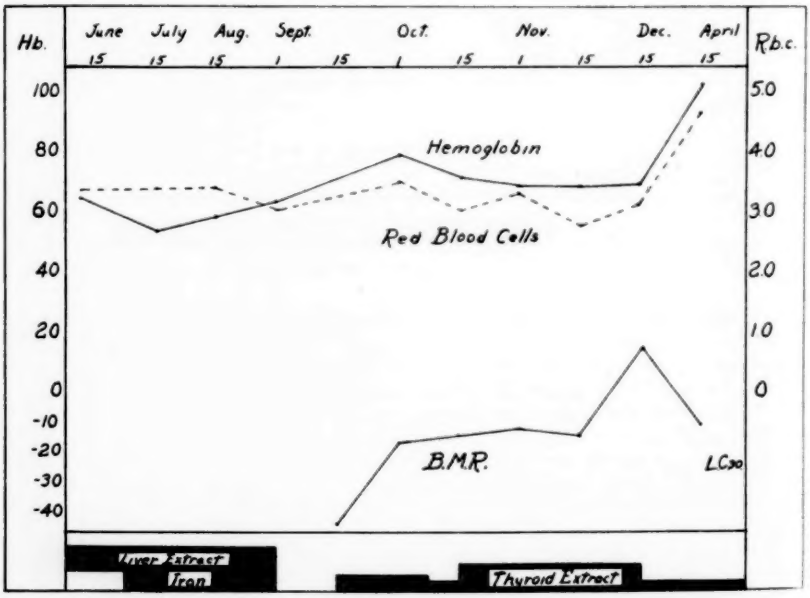
Hb.
June
July
Aug.
Sept.
Oct.
Nov.
Dec.
April
15 15 15 1 15 1 15 1 15 15 15
Rb.c.
100
80
60
40
20
0
-10
-20
-30
-40
5.0
4.0
3.0
2.0
1.0
0
Hemoglobin
Red Blood Cells
B.M.R.
LC30
Liver Extract
Iron
Thyroid Extract

FIG. 2 B

slowly increased and finally reached and remained within normal limits (Fig. 2 *B*). During this time, there was no significant change in either the mean corpuscular volume or hemoglobin content of the red blood cells. There was a progressive decrease of the icterus index. The achlorhydria persisted. The tongue regained its normal appearance and the paresthesias disappeared with return of the blood counts to normal.

CASE 3.—Mr. G. O., a 28-year-old white male patient of Drs. F. W. Niehaus and W. D. Wright, complained of weakness, fatigue, and chilly sensations for 1 year. When examined, September 4, 1935, no abnormality could be found except for a slight pallor. There were no tongue or neurologic changes.

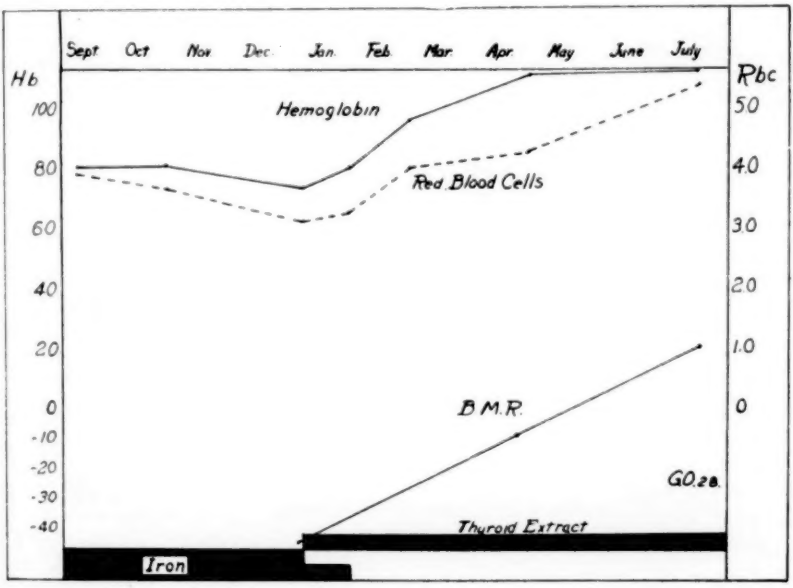

FIG. 3

The hemoglobin was 82% (14.2 gm.), the red blood cells 4,100,000, with a normal total and differential white blood cells count. For the next 4 months, the symptoms persisted in spite of 45 grains of iron and ammonium citrate daily. The anemia progressed to 76% (13.2 gm.) hemoglobin, and 3,250,000 erythrocytes. Further study of the blood then revealed the mean corpuscular volume to be 92 cu. microns, and the mean corpuscular hemoglobin 41 micromicrograms. The icteric index was normal. There was free hydrochloric acid present in the gastric analysis.

At this time, the possibility of hypothyroidism was recognized; the basal metabolic rate was −37%. Iron medication was then discontinued and thyroid extract, 2 grains daily, substituted. The improvement in the blood was roughly parallel to the increase in the metabolic rate and the patient's general well being. After 6 months of thyroid extract, the hemoglobin was 106% (20.2 gm)., and the erythrocytes 5,470,000 (Fig. 3).

CASE 4.—Mrs. S. P., a 53-year-old white female patient of Dr. E. J. Kirk, was first seen January 7, 1935, presenting typical symptoms and signs

of myxedema of about 6 years' duration. In addition, there was a moderate hypertension.

Before thyroid medication, the blood counts were normal with a hemoglobin of 88% (18.9 gm.), erythrocytes 4,500,000 and leukocytes 6400 with a normal differential formula. Hematocrit determinations were not made on this patient. Free acid was present in normal amounts in the gastric analysis. The basal metabolic rate was −25%.

Three weeks after a daily dose of 4 grains of thyroid extract, the metabolic rate had increased to +20%, but the hemoglobin had dropped to 69% (11.7 gm.), and the red blood cells to 3,700,000. Two months later, the blood returned to its previous normal level (Fig. 4).

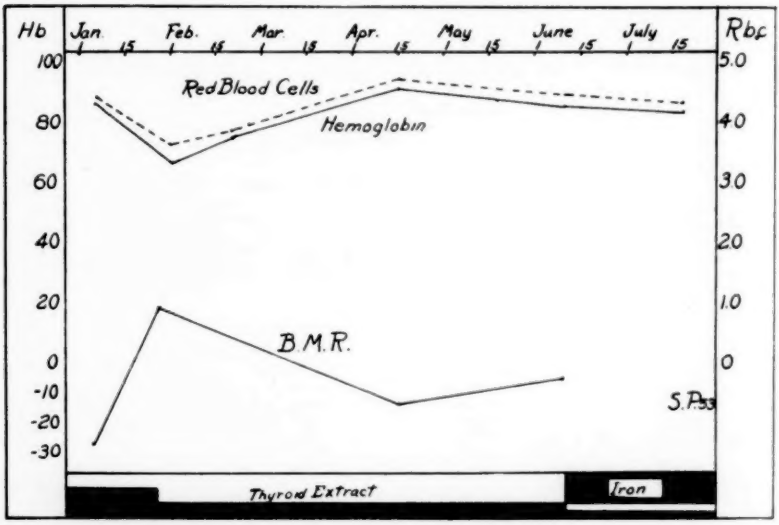

FIG. 4

CASE 5.—Mrs. M. C., a 50-year-old white female, entered the Outpatient Department, January 3, 1934, presenting the characteristic symptoms and signs of a severe hypothyroid state. After a subtotal thyroidectomy for a toxic adenoma, 4 years previous to entrance, she had gained 70 pounds in weight.

A blood count was not done on her first examination. The basal metabolic rate was −31%. She was advised to take a daily dose of 6 grains of thyroid extract. When the metabolism reached normal levels, 1 month later, this dose was decreased to 3 grains a day. Though most of her symptoms of myxedema quickly disappeared, the pallor, glossitis, and paresthesias of the hands and feet persisted.

Examination of the blood at this time revealed the hemoglobin to be 68% (11.5 gm.), the red cells 3,550,000, and the leukocytes as 6200 with a normal differential. Hematocrit determinations were not done, but from the blood smear, the erythrocytes appeared to be microcytic in character. There was no free acid found in the gastric content. Iron, in the form of Blaud's, 10 grains 3 times a day, was added to the thyroid extract; but after 5 months, there had been very little effect on the blood. The hemoglobin was 71% (12 gm.), the red blood cells 3,880,000 and the leukocytes 7600. The

mean corpuscular volume was 72 cu. microns, the mean corpuscular hemoglobin was 26 micromicrograms. The basal metabolic rate at this time was −12%. In order to facilitate better absorption of iron in the gastrointestinal tract, hydrochloric acid was given in conjunction with iron and ammonium citrate, 90 grains a day. This procedure seemed to result in a prompt improvement in the blood count to normal values and greatly improved the glossitis and paresthesias. However, because of a misunderstanding of orders, the patient did not receive any thyroid extract for 1 month, and then for several more months, inadequate doses, all of which resulted in a progressive decrease of the basal metabolic rate to −24% and the return of many unpleasant symptoms.

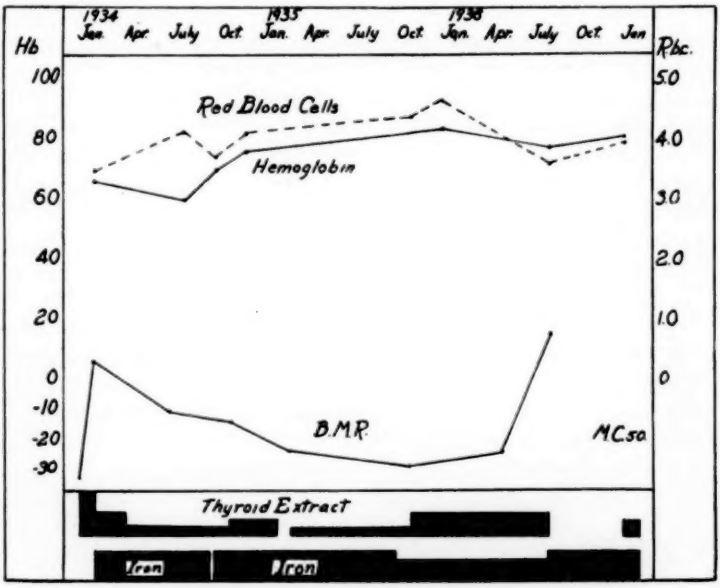

FIG. 5

The blood counts remained within normal limits in spite of this long period of hypometabolism. Again, however, with an increase of thyroid medication and the raising of the metabolism, the blood counts showed a transient decrease (Fig. 5).

Discussion. Though it was not a prominent feature, Stone[24] found anemia present in 56% of his 23 myxedematous patients, and in Lerman and Means'[14a] series, anemia was noted in 60% of the cases. The incidence of anemia in myxedema was not quite as high in our series of cases (44%). In our first 4 cases, the myxedema was classed as "spontaneous" in origin; in the remaining case, the hypothyroidism followed subtotal removal of the thyroid gland. All our cases were adults, 4 females and 1 male.

Etiology. The etiology of the anemia of myxedema is still an unsettled question. It is not known why anemia develops in approx-

imately one-half the cases of myxedema, whereas in the other half, equally as severe, the blood remains normal. Our observations are in accord with Emery's[5] who found no relation between the degree of anemia and the metabolic rate, or the duration of the disease. Lerman and Means[14b] add that 53% of their patients with myxedema showed an achlorhydria, and that the anemia is more likely to develop in those patients. Of our 20 patients, 11 had an analysis of their gastric juice, with 5 showing achlorhydria (45%). Though all 5 cases were associated with an anemia, in the other patients presenting as severe an anemia, the gastric acidity was normal. In our opinion, achlorhydria may very well serve as a conditioned deficiency in accentuating the production of anemia, but it is apparently not absolutely essential in the etiology.

MacKenzie,[17] Stone[24] and Minot[20] believe that the anemia results from a deficient manufacture of blood cells in the bone marrow due to the sluggish oxidation that occurs in all tissues during the hypometabolic state. This explanation seems substantiated, experimentally, by Esser,[6] Orr,[21] Kunde, *et al.*,[12] and ourselves,[23a, b] all working with totally thyroidectomized rabbits, and uniformly producing an anemia that responded to thyroid extract.

The question naturally arises as to whether a plasma volume shift with a resulting hydremia could possibly account for the blood changes in myxedema. That this is not the case, and that the anemia in myxedema is real and not apparent is based on the work of Friedländer *et al.*,[7] who found a sharp decrease in blood volume following thyroidectomy in male cats. Moreover, Thompson[26] concluded from his clinical observations that, 1, in myxedema, as the weight increases, the total plasma volume decreases; and 2, in myxedema, there was frequently a decrease of total blood volume of 25%. This total plasma and blood volume decrease in myxedema should then cause a concentration of the cellular content of the blood, and not, as in some cases of myxedema, a low hemoglobin and erythrocyte count. Though this possibility of a blood volume shift is now under our investigation, it is probably not the explanation of the anemia of myxedema. However, a plasma volume increase in myxedema following the administration of thyroid extract may explain the transient decrease of hemoglobin and erythrocytes that we so often noted during the first few weeks of therapy. This decrease is well exemplified in Case 4, and to a much lesser degree in Cases 1, 2, and 5.

Symptoms and Signs. In addition to the usual characteristic features of myxedema, the anemic patient may present such clinical manifestations as a light lemon-yellow pallor, glossitis, and paresthesias. The icteric tint of the skin is not due to increased bile pigment in the blood stream, as is the case in pernicious anemia or familial hemolytic anemia.[20] In our group, the icterus index was normal in 3 cases, moderately elevated in 1 case and not determined

in the remaining patient. We have observed the fiery-red, sore tongue in 1 patient (Case 5), and the bald, smooth, pale tongue in 2 others (Cases 1, 2). Pitfield[22] and Means, Lerman and Castle[19] have commented on the neurologic manifestations of myxedema. In our series, numbness and tingling of the hands and feet were present in 3 patients (Cases 1, 2, 5). In each instance, the reflexes were present, but diminished; the vibratory sense was absent in 1 and present in the 2 others. Four months of intensive parenteral liver extract failed to cause any change in these neurologic signs in Case 2, although thyroid extract caused marked improvement in this and in the other 2 cases.

Blood Picture. The reported blood picture in this type of anemia has not been uniformly constant or characteristic. Usually, the degree of anemia is not very marked. The hemoglobin is usually between 50 and 70%; the number of erythrocytes between 3 and 4 million. The reticulocytes are not increased. Some writers have compared the erythrocytes to those found in chlorosis,[2,27] while others,[3,17,22,24] have been impressed with the resemblance of this anemia to that of pernicious anemia. Lerman and Means[14] are of the opinion that the anemia may be classed in either group, and that in those patients having achlorhydria, a pernicious instead of the secondary type of anemia may develop.

Experimentally, Kunde *et al.*,[12] working with cretin rabbits, and in our work with the adult animals,[23a] the anemia was characterized in each instance by a definite macrocytosis and hyperchromia. We have not, however, observed this erythrocytic change clinically; as in the 4 cases in which hematocrit observations were made, 3 showed the mean corpuscular volume and the mean corpuscular hemoglobin to be within the limits of normal variation, *i. e.*, normocytic and normochromic. In the other instance (Case 5), a postoperative case, there was a definite hypochromia present. In this case, the existing achlorhydria may have been a factor in producing, accentuating, or changing the character of the red blood cells through an iron-deficiency. It is obvious that additional hematocrit observations on a large series of myxedematous patients with anemia are necessary before the erythrocyte is definitely classified as normocytic in character.

The discrepancy between the experimental and clinical observations of red blood cell size and hemoglobin content in myxedema may be due to several important factors. In the first place, the amount of functioning thyroid tissue must be considered. Experimentally, we are dealing with animals that have been subjected to a *total* thyroidectomy, following which *each* animal developed an anemia. On the other hand, the majority of the clinical cases of myxedema have been *spontaneous* in origin, and approximately only *half* of these patients develop anemia. Furthermore, in the clinical cases, the presence or absence of the complex diet factors,

gastric achylia, pregnancies, and chronic infectious and toxic processes, and their effect on the hematopoietic system must all be kept in mind. Experimentally, these factors do not complicate the blood picture as we deal with young, healthy animals, of approximately the same age and weight, on a standard diet and under ideal environmental surroundings.

Usually, there is little or no definite change in the leukocyte count or the differential formula, although a slight leukopenia with a slight lymphocytosis may be present. Minot[20] concluded that a decreased bone-marrow function was evident, because the anemia was characterized by a moderate leukopenia, a slight lymphocytosis, and often a decrease of the platelet count, without evidence of increased reticulocyte formation. One would certainly not ascribe the anemia to increased blood destruction in the absence of increased bilirubinemia. To explain the anemia, it may help to study bone marrow biopsies in the clinical cases, and though we have completed such a study in our thyroidectomized rabbits, both before, during and after thyroid feedings, we have not yet arrived at any definite conclusions.

Differential Diagnosis. In the presence of an "anemia," achlorhydria, tongue changes and paresthesias, an erroneous diagnosis of pernicious anemia may be made instead of the anemia of myxedema. Such was our experience in Case 2. Sturgis[25] and Minot[20] believe that though there is a close clinical similarity between the two, the actual erythrocytic changes in myxedema are different in that the large macrocytes are absent. In our experience, the use of the hematocrit to determine the average corpuscular volume and hemoglobin content of the red blood cells is of utmost value in the differential diagnosis. Furthermore, the presence of a normal gastric acidity and the physical signs of myxedema aid in ruling out pernicious anemia. Of course, the diagnosis of both pernicious anemia and myxedema in the same individual has been made.[16,19] As mentioned, we have 3 such cases under observation. However, the association must be rare as Giffin and Bowler[8] found only 2 cases of myxedema in the analysis of 628 cases of pernicious anemia. The basal metabolic rate in pernicious anemia is ordinarily normal or slightly increased.

Treatment. Most writers have observed that the anemia of myxedema improves under thyroid therapy. Lerman and Means[14a] conclude that thyroid extract alone is sufficient to cause the anemia to disappear slowly, but that iron, in addition to the thyroid extract, accelerated regeneration of the blood if hypochromia persists, and that liver extract is given in those cases with a blood picture of pernicious anemia.

Our experience, both clinically and experimentally, has led us to believe that neither liver extract nor iron, alone or in combination, is of any real value in treating the anemia of myxedema. It has been

noted that intensive intramuscular liver extract failed to cause any reticulocyte response in either Case 1 or 2. Also, in spite of adequate doses of iron, Case 3 developed his anemia while under observation. Only in Case 5 who had a definite hypochromia did iron seem indicated and which probably accelerated blood formation. In each case, thyroid extract stimulated hemapoiesis with improvement in the blood, though we have been impressed with the slowness of the process.

These clinical observations are directly comparable to the experimental findings that we observed in myxedematous rabbits, *i. e.*, a definite reticulocyte response of 8 to 14% on the fifth to seventh day following varying doses of thyroid medication, with a later, slow, but sustained rise in the hemoglobin and the number of red blood cells.[23b] Such a response did not occur with either iron or intramuscular liver extract. Furthermore, direct experimental evidence of bone marrow stimulation by thyroid extract has been reported by Kunde *et al.*,[12] Limm *et al.*,[15] Adams and Shevket,[1] and Latta and Benner.[13]

Summary. 1. The exact etiology of the anemia of myxedema is unknown, but it is probably the result of decreased blood formation, due to the hypometabolic effect on the bone marrow.

2. In addition to the usual physical signs of myxedema, the anemic patient may present such clinical features as a lemon-yellow pallor, glossitis, paresthesias, and an achlorhydria. An erroneous diagnosis of pernicious anemia may be made.

3. In 3 cases, the mean corpuscular volume and the hemoglobin content of the red blood cells showed that the anemia was normocytic and normochromic in character. In the fourth case an achlorhydria, hypochromia and microcytosis may have been due to an associated iron-deficiency anemia.

4. Though thyroid extract causes a prompt increase in the basal metabolic rate, a transient decrease in the blood count may first be noted, followed by a slow, and sustained rise in both hemoglobin and erythrocytes.

5. In the presence of hypochromia, iron may accelerate the regeneration of blood cells, but liver extract appears to be of no value in this type of anemia.

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THE SEDIMENTATION RATE IN ANGINA PECTORIS AND CORONARY THROMBOSIS.*

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The erythrocyte sedimentation rate has been found elevated in coronary thrombosis,[9] and it has been suggested that this finding may be of value in diagnosis, prognosis and treatment. The present communication presents a comparison of the rate of red blood cell sedimentation in cardiac infarction and angina pectoris. The purpose is to ascertain the value of the test and to obtain further information concerning the underlying pathologic processes.

Methods. The erythrocyte sedimentation rates were determined according to the method of Rourke and Ernstene.[10] "The corrected sedimentation index," according to this method, is the maximum rate of settling of the red blood cells, corrected for the percentage volume of erythrocytes in the blood specimen; the normal for young adults lies between 0.08 and 0.35 mm. per minute. The fibrinogen content of the plasma was measured by the method of Wu;[15] the serum cholesterol by the method of Ling.[8]

The patients with angina conformed to those described by Heberden.[5] The diagnosis was confirmed in each case by observation during an attack. So far as could be determined, they suffered from no illness other than coronary artery disease. All patients had been observed in this clinic at weekly intervals for months or years and their clinical courses were well known.

The diagnosis in the cases of coronary thrombosis was established by the characteristic history, clinical course and changes in electrocardiographic tracings. Therapy in these cases included 3 weeks' complete bed rest in

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the hospital and whenever possible 3 additional weeks at home or in a nursing home. Blood was obtained from these patients as soon after entrance to the hospital as was feasible and once or twice a week thereafter until discharge or until the index had returned to normal. Additional tests were made in some patients several months after discharge from the hospital.

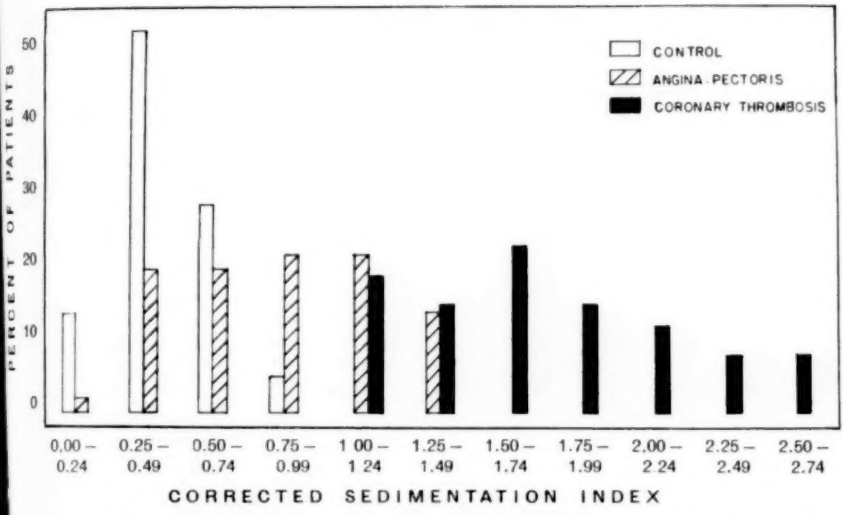

FIG. 1.—The corrected sedimentation rate in 21 healthy persons 45 to 70 years of age, 55 patients with angina pectoris and 37 patients 4 to 12 days after the onset of coronary thrombosis.

Results. *Controls.* It has been suggested that the sedimentation rate may be increased in old age, arteriosclerosis and hypertension.[7,16] No figures obtained by the methods employed in this investigation are available in this group of subjects. Consequently the corrected sedimentation indices of 21 persons aged 45 to 70 were studied (Fig. 1). All these persons were working and apparently healthy, although they showed varying degrees of arteriosclerosis and several had moderate hypertension. Of these subjects, two-thirds had an index below 0.50, 1 had an index greater than 0.70, the remaining indices were 0.50 to 0.70. It is evident that individuals in this age group without evidence of disease may have sedimentation indices somewhat higher than the accepted normal for young adults; indices up to 0.70 are apparently normal.

Coronary Thrombosis. Coronary thrombosis was studied in 25 men and 12 women: 27 had a history of angina pectoris in the past; 1 patient was in the fourth decade of life, 7 were in the fifth, 16 in the sixth, 11 in the seventh and 2 were in the eighth. The sedimentation indices of 2 patients, measured within 10 hours after the onset of symptoms, were 0.95 and 1.35; the indices of three

others, measured within 24 hours of the onset of pain, were 0.53, 0.55 and 1.20.

During the first few days after the onset of an attack of coronary thrombosis, the sedimentation rate increased rapidly; 83% of the patients studied developed indices greater than 1.0 before the fourth day. The maximum increase was found between the fourth and twelfth day at which time all sedimentation indices were higher than 1.0 and 66% of the indices were greater than 1.5 (Fig. 1). After 12 days the frequency of relatively low sedimentation rates increased; after 21 days indices less than 1.0 were found in 60% of patients (Table 1).

TABLE 1.—THE SEDIMENTATION RATE IN CORONARY THROMBOSIS AT VARIOUS TIME INTERVALS AFTER THE ONSET OF SYMPTOMS.

Days after onset of symptoms.	Corrected sedimentation index. 0.28 to 0.49.	0.50 to 0.99.	1.00 to 1.49.	1.50 to 1.99.	2.00 to 2.60.
	Per cent of patients.				
1–4	0	17	**50**	25	9
5–9	0	0	30	40	**30**
10–14	0	20	25	**45**	10
15–19	5	36	36	18	5
20–24	14	**48**	14	14	10
25–30	**33**	28	19	10	10

In 13 instances the rate returned to normal (less than 0.70 mm. per minute) between 14 and 28 days after the onset of symptoms. In 19 patients the index was still elevated at the time of discharge (22 to 32 days after the onset of the disease). The remaining 5 patients died in the hospital during the acute attack (Fig. 2); these patients had indices of 1.0 to 1.75 1 to 3 days before death.

Patients with pulmonary infarction usually had a rapid sedimentation rate, but similarly increased indices were observed in patients without evidence of pulmonary complications.

Angina Pectoris. The sedimentation rate was studied in 55 patients (43 men and 12 women) with angina pectoris in whom the duration of the disease varied from 3 weeks to 10 years. Three patients were in the fourth decade of life, 8 were in the fifth, 31 in the sixth and 13 in the seventh. Approximately one-half the patients had electrocardiographic evidence of coronary artery disease, an equal number had hypertension and about one-third had cardiac enlargement by Roentgen ray.

In 21 patients the sedimentation indices were 0.70 or less; in the remainder (62%) the values were between 0.73 and 1.38 (Fig. 1). The sedimentation index tended to be 0.70 or lower in those patients whose symptoms were less than 6 months in duration. Hypertension, cardiac enlargement (Roentgen ray) electrocardiographic evidence of coronary artery disease, or a history of preceding coronary occlusion did not influence appreciably the frequency of low sedimentation indices nor was there any evidence that patients

with angina at rest tended to have higher indices than patients with angina only on exertion (Table 3).

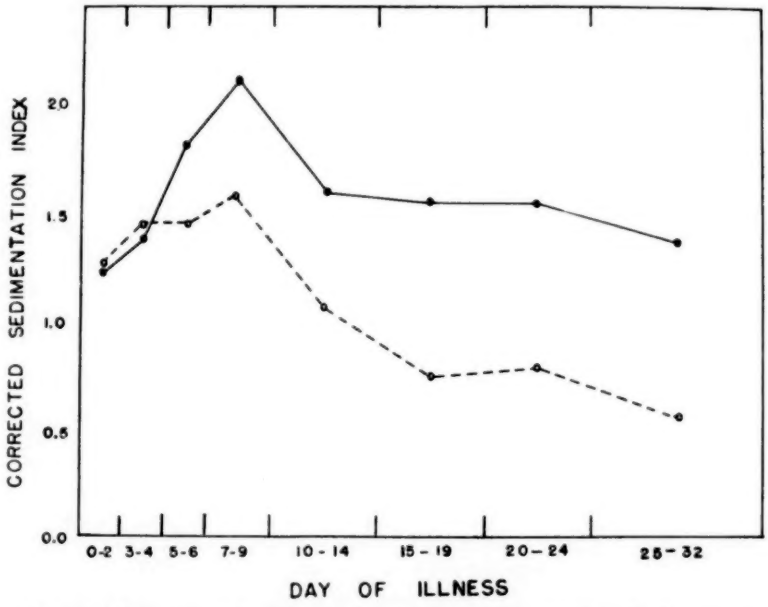

FIG. 2.—The corrected sedimentation index in coronary thrombosis. o——o, composite curve of 13 patients whose sedimentation rates returned to normal within 4 weeks after the onset of symptoms. ●——●, composite curve of 19 patients whose sedimentation rates failed to return to normal by 28 days.

TABLE 2.—THE CORRECTED SEDIMENTATION INDEX IN 31 PATIENTS WITH CORONARY THROMBOSIS 6 TO 12 MONTHS AFTER DISCHARGE FROM THE HOSPITAL.

Corrected sedimentation index at time of discharge.	Clinical condition 6 to 12 months after discharge from hospital.		
	Dead.	Cardiac* symptoms.	No cardiac symptoms.
	Per cent of patients.		
0.28–1.00 (13 patients)	15	54	31
1.10–2.38 (18 patients)	39	39	22

* Angina pectoris, congestive failure or cardiac asthma.

In 20 patients the sedimentation rates were measured again after an interval of 1 to 26 months. In 10 instances there were increases of 0.38 to 1.76 mm. per minute (50% to 300%). Five of these patients had had a definite increase in the severity of symptoms within 2 weeks prior to the repetition of the test. Three had shown a striking decrease in symptoms during the preceding 2 weeks; the remaining 2 had shown no apparent change in clinical condition. Subsequent determinations in these patients showed a decrease of the sedimentation index toward the previous level. An eleventh

patient developed congestive failure during the period of observation; with the onset of edema there was a decrease in the sedimentation rate. Repeated determinations in the remaining 9 patients showed a change of less than 0.30 mm. per minute (33% or less). In none of these patients was there any evidence of recent change in clinical condition.

TABLE 3.—FREQUENCY OF LOW SEDIMENTATION RATES (CORRECTED SEDIMENTATION INDEX) IN PATIENTS WITH ANGINA PECTORIS.

		No. of patients studied.	Per cent of patients with C. S. I. less than 0.7.
Duration of symptoms:	Less than 6 months	12	75
	18 months to 9 years	33	33
Type of angina:	Only on exertion	34	41
	At rest as well as on exertion	21	38
Previous coronary thrombosis:	No evidence in history	39	45
	Definite history of attack	16	31
Blood pressure:	Normal	28	46
	Hypertension	26	31
Heart size (7-foot roentgenogram):	No enlargement	29	59
	Enlargement	19	31
Electrocardiogram:	No evidence of coronary disease	25	48
	Evidence of coronary disease	28	36
Serum cholesterol:	184–250 mg. per 100 cc.	19	31
	255–413 mg. per 100 cc.	16	56

Comment. It is generally agreed that the rate of sedimentation of the red blood cells is increased in the presence of infection or tissue damage and is an index of the severity of the processes involved. It is to be expected, therefore, that coronary thrombosis and the resulting myocardial infarction will be accompanied by an abnormally rapid sedimentation rate. Measurements of the sedimentation rates of 58 cases of coronary thrombosis have been reported in the literature;[1,2,7,9,12,14] the present communication adds 37 more. In every instance the sedimentation rate was abnormally rapid at some time during the course of the disease. Thus, it would appear that a rapid sedimentation rate is one of the most constant manifestations of coronary thrombosis.

In 1931, Rabinowitz, Shookhoff and Douglas[9] suggested that the test "may be valuable in diagnosis in cases appearing for examination a number of days after an attack and presenting a normal temperature and blood count. . . . Repeat determinations . . . may aid materially in prognosis and treatment. . . . It appears advisable to keep a patient in bed for at least as long as the sedimentation time still suggests active myocardial changes." We have been unable to find any report concerning the value of the procedure in actual practice.

The test frequently helps in differentiating between coronary thrombosis and severe paroxysms of angina pectoris. This is especially true if the patient is seen for the first time several days or a week after the episode. Under such conditions it may be

impossible to ascertain whether fever, leukocytosis or changes in the electrocardiogram have taken place. A persistently normal or only slightly increased sedimentation rate between the fourth and twelfth day after the attack is strong evidence that there has been no myocardial infarction. Conversely, a marked increase in sedimentation rate, especially if the rate shows progressive changes from day to day, may be of distinct aid in establishing the diagnosis of coronary occlusion. It must be remembered, that patients with angina pectoris may show an elevated sedimentation index. This rarely reaches as high as 1.40, whereas patients with coronary occlusion usually have indices greater than 1.50. The test is, of course, of no value in differentiating between myocardial infarction and tissue damage elsewhere such as may occur in gall bladder disease.

We have found the test an aid in following the course of the disease but of little value in predicting the outcome of the acute attack. The period during which the sedimentation rate is rapid corresponds to the period when the maximum myocardial softening occurs. The period of recovery and healing of tissue damage is accompanied by a decrease in the sedimentation rate. The sedimentation indices of the 5 patients who died during the acute attack differed in no way from those of many who recovered. Those patients who were discharged from the hospital with elevated sedimentation rates, however, had a mortality more than twice as great as those who had low indices on discharge (Table 2).

It must be remembered that the underlying coronary arteriosclerosis predisposes to recurrent thrombosis. The best of management will not, therefore, eliminate a certain inevitable mortality. It would seem advisable, however, to continue bed rest until complete cicatrization of the myocardial infarct has probably taken place. The length of time necessary for this is not known. Large areas undoubtedly take longer than small ones. Regions of residual softening have been observed many weeks after the acute attack. Five weeks after the onset of symptoms 40% of our patients still showed high sedimentation rates. We have observed indices of 0.95 to 1.25 several months after discharge from the hospital. In the light of these facts it would seem advisable to continue bed rest until the sedimentation rate either returns to normal or shows no further progression towards normal.

Little is known concerning the sedimentation rate in angina pectoris. Burak[2] found the rate normal in 9 ambulatory cases of "severe" angina. Wood[14] found normal rates in 6 cases of "angina of effort," whereas 5 cases of "angina of rest" showed a slight or moderate increase in rate. These 20 cases were studied by the Westergren method, without correction for the hematocrit. The hematocrit of approximately one-half of our patients with angina was greater than the average normal. This increase in hematocrit,

although slight, tends to diminish the total fall in the first hour for not only does it slow the rate at which the red cells settle but it also prolongs the time before obvious sedimentation begins.[10] A close correlation between the corrected sedimentation index and the plasma fibrinogen content has been demonstrated in rheumatic fever[3] and in a large number of other pathologic conditions.[4] Essentially this same correlation was found in 15 of our patients with angina in whom the plasma fibrinogen was determined. Ham[5] has observed an increased sedimentation rate in the defibrinated blood of some patients with markedly increased serum cholesterol. Approximately half of our patients with angina pectoris had a moderate elevation of the serum cholesterol level (250 to 415 mg. per 100 cc.); however, no correlation between the sedimentation rate and the serum cholesterol content was observed (Table 2).

Certain facts suggest that attacks of angina pectoris occasionally result in tissue damage. The occurrence of abnormalities in the electrocardiogram indicates that myocardial changes have taken place, and it has been demonstrated that areas of myocardial softening can occur even in the absence of occlusion of the coronary arteries.[11] During the first few months after the onset of angina the sedimentation rate is likely to be normal, later in the course of the disease it becomes more rapid. Sudden changes in the severity of the disease are not infrequent and such changes may be accompanied by a striking increase in the rapidity of red cell sedimentation.

It is evident that knowledge of the sedimentation rate may be of value in examining and following the course of patients with angina pectoris or coronary thrombosis. It must be remembered, that the test is not specific for these conditions and a single determination of the sedimentation rate, without knowledge of the clinical findings and without assurance that other tissue damage or infection is absent, is of little value.

Summary and Conclusions. 1. The corrected sedimentation index was studied in 113 persons: 37 with coronary thrombosis, 55 with angina pectoris, and 21 apparently normal persons between the ages of 45 and 70.

2. Elderly individuals, without any evidence of disease, may have a corrected sedimentation index slightly higher (up to 0.70) than the accepted normal for young adults.

3. A moderate elevation of the corrected sedimentation index (0.73 to 1.38) was found in over half of the patients with angina pectoris. There is reason to believe that attacks of angina pectoris occasionally result in myocardial damage.

4. An elevated sedimentation rate is one of the most constant manifestations of coronary thrombosis. The fastest rates were observed between the fourth and twelfth days after the onset of symptoms.

5. In two-thirds of the cases the rate was considerably greater

than that seen in angina pectoris; this may be of value in differentiating between angina pectoris and coronary occlusion during the first 2 weeks after the onset of an attack.

6. The sedimentation rate reflects the course of the disease and is an aid in following the progress of the patient but is of little or no aid in the prognosis of the acute attack.

7. The mortality of patients discharged from the hospital with fast sedimentation rates was twice as great during the first year after discharge as that of patients discharged with low or normal rates. It is advisable to continue bed rest until the sedimentation index either returns to normal or shows no further progression towards normal.

We wish to express our appreciation to Dorothy Rourke Gilligan for her kind interest and coöperation in these studies.

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FRACTIONATION STUDIES ON INTRINSIC FACTOR IN NORMAL HUMAN GASTRIC JUICE.

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It has been demonstrated[10b,14,17] that the incubation of liver or liver extract with normal human gastric juice or hog gastric tissue markedly increases the potency of liver or liver extract. This increase is probably the result of the interaction of the intrinsic factor of Castle[2] in the gastric juice or tissue with an extrinsic factor present in the liver. There is, however, a definite relation-

ship between the amounts of liver extract and gastric juice necessary to produce maximal reticulocyte responses when the combination is fed daily by mouth to patients having pernicious anemia. Near maximal responses do not follow the administration of smaller amounts than 4 gm. of liver extract (that derived from approximately 90 gm. of whole liver) even after it has been incubated with 100 cc. of gastric juice. To increase the potency of 4.5 gm. of liver extract satisfactorily, 50 or more cubic centimeters of gastric juice are required.[7b]

We have previously recorded a few of the properties of the intrinsic factor in normal human gastric juice. This factor can be concentrated by the use of ultrafilters.[10c] Most of the intrinsic factor is destroyed or used up during the process of concentration by vacuum distillation. The hematopoietic material in concentrated human gastric juice active on intramuscular injection, however, is formed during this process.[7a] Our previous studies also confirmed the work of Castle and his associates[2] in that the intrinsic factor can be separated from the enzymes pepsin and rennin by casein precipitation. However, casein precipitation is not a satisfactory method for the removal of these enzymes in the isolation of the intrinsic factor. A small amount of the casein is dissolved in the gastric juice, thus introducing an extraneous protein. In addition, the removal of the last traces of pepsin and rennin with casein is quite difficult.

It is the purpose of this paper to record additional information on the properties of the intrinsic factor and the methods employed in attempting to obtain the intrinsic factor in a purer state. In many of the following studies the gastric juice was concentrated by ultrafiltration before any attempts were made at fractionation of the gastric juice. This was of great assistance, as many of the procedures would have been much more difficult, or even impossible, without preliminary concentration of the gastric juice.

Methods. All patients used in these studies were clinically and hematologically typical of pernicious anemia. On entering the hospital, the patients were placed on low vitamin B complex diet containing no meat, eggs, or milk. Daily red blood cell counts, hemoglobin determinations (Newcomer), and reticulocyte counts were made. During the peak of the rise the reticulocytes were counted twice daily. Control periods of 2 to 7 days preceded the institution of the test therapy. Following the administration of the test materials, all patients received either "Extralin" (Liver-Stomach Concentrate, Lilly) or liver extract by mouth.

The various fractions of gastric juice tested in these studies were brought to approximately the original volume with 0.3% HCl, and adjusted to pH 1.0 to 1.2, and the quantity of the material equivalent to the designated amounts was incubated for 2 hours with 1 vial of liver extract. These liver extract gastric juice digests were neutralized immediately before being administered to the patients at 4.30 P.M. The evening meal was served at 6.30 P.M. The digests were administered daily for 10 days except to Cases 4, 5, and 6, who received the digests for 15 days. This

prolongation of treatment was due to the fact that the reticulocyte responses following treatment of the gastric juice with alcohol were markedly delayed.

The ultrafilters used were of the Bechold type described by Bronfenbrenner[1] and used previously,[7a,10c] by us. The alcohol and acetone soluble portions of the gastric juice administered to Cases 3, 4, 6, and 7 were freed of the solvents by vacuum distillation as previously described[7a] immediately after removal of the precipitate. Casein precipitation was carried out as described previously.[10c] When Lloyd's reagent was added to the gastric juice, the gastric juice was stirred with a mechanical stirrer for from 15 to 30 minutes. If, after removal of Lloyd's reagent by centrifugation and filtration through paper, the gastric juice still contained rennet activity, more Lloyd's reagent was added and the procedure repeated until all rennet activity had been removed. The method[10a] used for determining rennet activity is extremely sensitive.

Results. Morris[12] and his associates reported that the hematopoietic material in concentrated gastric juice active on intramuscular injection was dialyzable and soluble in 80% acetone and 80% alcohol. We, however, found that the intrinsic factor in normal human gastric juice after concentration by ultrafiltration would not dialyze through a cellophane sack either before or after precipitation of the gastric enzymes with casein. (See Cases 1 and 2, Table 1.) The intrinsic factor remained in the sack. Fractionation of the concentrated gastric juice by alcohol and acetone was also found to be unsatisfactory as a means of purification of the intrinsic factor. The material is at least partially soluble in alcohol and acetone (Cases 3, 4, 6, and 7*a*). However, a good portion of the intrinsic factor is destroyed by the alcohol and acetone or by the process of vacuum distillation during the removal of the solvents. The alcohol precipitates contained a small amount of intrinsic factor (Case 5), but not enough to produce a second reticulocyte rise in Case 7*b* following the slight response this patient had had to liver—gastric juice digest in which the alcohol soluble portions of the same gastric juice were used as a source of intrinsic factor.

Northrop[13] was able to precipitate pepsin by the use of ammonium sulphate. We therefore hoped that the pepsin and rennin and mucus could be separated from the intrinsic factor by this reagent; however, the precipitate also contained the intrinsic factor. The precipitate formed by half saturation of 120 cc. of gastric juice with ammonium sulphate was redissolved in 0.3% HCl, incubated with 1 vial of liver extract, and fed daily to Case 8 (Table 2). A maximal reticulocyte response (14.5% at original red blood cell level of 2.17 million) and a satisfactory clinical improvement followed this therapy.

At the time it seemed strange that the intrinsic factor should be partially soluble in alcohol and yet be precipitated with ammonium sulphate. Dakin and West,[4] however, have subsequently shown that the active principle in liver extract has similar solubility. Although we knew that alcohol was injurious to the intrinsic factor,

we felt it was advisable to treat the material precipitated with ammonium sulphate with 80% alcohol. It was found (Cases 9 and 10) however that the intrinsic factor, after ammonium sulphate precipitation, was insoluble in alcohol. This change in alcohol solubility could be due either to the increase in salt content of the fluid after the ammonium sulphate precipitation or to the absence in the redissolved juice of some material in the original gastric juice which held the intrinsic factor in the alcohol.

TABLE 1.—RESPONSES OF RED BLOOD CELLS, HEMOGLOBIN AND RETICULOCYTE PERCENTAGES OF JUICE FRACTIONATED BY DIALYSIS AND

Case No.	1.			1.			2.			2.			3.		
Method used in fractionation of gastric juice	Dialyzed.*			Dialyzed.*			Pttd. with casein then dialyzed.*			Pttd. with casein then dialyzed.*			Pttd. with 80% acetone.*		
Fraction of gastric juice used	Dialysate.			Undialyzed.			Dialysate.			Undialyzed.			Filtrate.		
Cc. gastric juice derived from	120 cc.			120 cc.			120 cc.			120 cc.			120 cc.		
Day.	R. B. C., mill. per c.mm.	Hgb., † %.	Ret., %.	R. B. C., mill. per c.mm.	Hgb., %.	Ret., %.	R. B. C., mill. per c.mm.	Hgb., %.	Ret., %.	R. B. C., mill. per c.mm.	Hgb., %.	Ret., %.	R. B. C., mill. per c.mm.	Hgb., %.	Ret., %.
..	2.1	50	0.2	...	..	1.6	2.4	63	1.8	2.6	56	0.5	0.9	35	0.8
1	2.1	51	0.6	1.9	44	1.8	2.2	59	1.2	...	..	1.0	0.9	37	0.7
2	2.4	54	0.2	1.8	51	1.8	2.3	66	1.6	2.5	52	0.0	1.0	27	0.4
3	...	..	0.8	...	52	3.4	2.8	53	0.5	2.3	50	0.6	0.9	..	0.6
4	2.2	56	1.0	2.1	59	4.6	...	..	0.7	2.4	52	1.8	0.9	26	1.2
5	2.2	55	1.2	1.8	59	4.4	2.4	66	1.0	2.5	53	1.8	0.8	23	2.0
6	2.3	55	2.4	2.1	..	7.0	2.5	54	0.9	2.5	54	3.2	0.9	28	2.1
7	2.1	52	2.9	...	..	8.0	2.5	59	1.0	2.7	60	2.9	0.9	25	5.2
8	2.1	44	2.0	2.5	59	7.1	2.5	53	0.0	..	..	3.5	1.1	29	7.5
9	1.8	45	2.8	2.4	66	7.2	2.4	58	0.2	2.6	61	2.3	1.1	27	7.5
10	...	..	1.6	2.6	64	4.5	2.6	56	0.5	2.6	49	2.0	...	..	6.3
11	...	..	...	2.3	71	2.1	...	..	...	...	..	...	1.1	34	6.1
12	...	..	...	...	..	...	...	..	...	...	..	...	0.9	32	6.0
13	...	..	...	...	..	...	...	..	...	...	..	...	1.0	30	3.8
14	...	..	...	...	..	...	...	..	...	...	..	...	1.1	27	2.0
15	...	..	...	...	..	...	...	..	...	...	..	...	...	..	...
16	...	..	...	...	..	...	...	..	...	...	..	...	...	..	...
17	...	..	...	...	..	...	...	..	...	...	..	...	...	..	...
18	...	..	...	...	..	...	...	..	...	...	..	...	...	..	...
19	...	..	...	...	..	...	...	..	...	...	..	...	...	..	...
20	...	..	...	...	..	...	...	..	...	...	..	...	...	..	...
Daily therapy				Liver extract, 3 vials.						"Extralin," 12 capsules.			"Extralin," 10 capsules.		
Day.															
..	...	..	...	2.3	71	2.1	...	..	...	2.6	49	2.0	1.1	27	2.0
1	...	..	...	2.5	66	3.6	...	..	...	2.6	50	1.1	1.3	34	3.4
2	...	..	...	2.8	69	4.3	...	..	...	2.4	51	2.0	1.6	37	...
3	...	..	...	2.8	69	2.2	...	..	...	2.5	49	1.5	...	..	3.0
4	...	..	...	2.3	69	1.1	...	..	...	2.8	53	1.0	1.3	34	5.0
5	...	..	...	2.7	72	3.1	...	..	...	...	..	3.2	1.5	37	6.0
6	...	..	...	3.1	77	3.3	...	..	...	3.0	56	2.0	1.7	45	13.2
7	...	..	...	3.3	68	2.6	...	..	...	2.7	48	1.8	1.6	41	10.2
8	...	..	...	3.5	72	1.0	...	..	...	2.9	51	1.1	1.5	41	14.0
9	...	..	...	...	..	1.2	...	..	...	3.0	50	2.0	1.4	..	14.0
10	...	..	...	...	..	2.5	...	..	...	2.9	51	1.8	...	..	14.8
11	...	..	...	3.3	83	1.6	...	..	...	3.0	55	1.0	1.5	52	14.0
12	...	..	...	3.1	78	...	...	..	...	...	..	2.7	1.6	48	13.0
13	...	..	...	...	..	...	...	..	...	3.3	78	1.4	2.0	49	11.0
14	...	..	...	...	..	...	...	..	...	3.2	82	0.2	2.2	50	7.6
15	...	..	...	...	..	...	...	..	...	...	..	...	2.6	59	8.6
16	...	..	...	...	..	...	...	..	...	...	..	...	2.7	59	6.7
17	...	..	...	...	..	...	...	..	...	...	..	...	...	..	5.5
18	...	..	...	...	..	...	...	..	...	...	..	...	2.9	69	4.1

* Gastric juice concentrated by ultrafiltration previous to fractionation.
† Newcomer method.

An attempt was then made to precipitate the enzyme-free casein supernatant fluid, which has been shown to contain the intrinsic factor,[10c] with ammonium sulphate in the hope that the casein left in the fluid could be precipitated out leaving the intrinsic factor in solution. The intrinsic factor, however, was precipitated with the casein by the ammonium sulphate. The liver extract gastric juice digest made with the redissolved precipitate from 150 cc. original gastric juice apparently contained a considerable amount of ammo-

PERNICIOUS ANEMIA PATIENTS TO LIVER EXTRACT-GASTRIC JUICE DIGESTS MADE FROM GASTRIC BY 80% ALCOHOL AND 80% ACETONE.

4.			5.			6.			7a.			7b.		
Pttd. with 80% alcohol.*			Pttd. with 80% alcohol.*			Pttd. with 80% alcohol.*			Pttd. with 80% alcohol.*			Pttd. with 80% alcohol.*		
Filtrate.			Precipitate.			Filtrate.			Filtrate.			Precipitate.		
120 cc.			120 cc.			150 cc.			150 cc.			150 cc.		
R. B. C., mill. per c.mm.	Hgb., %.	Ret., %.	R. B. C., mill. per c.mm.	Hgb., %.	Ret., %.	R. B. C., mill. per c.mm.	Hgb., %.	Ret., %.	R. B. C., mill. per c.mm.	Hgb., %.	Ret., %.	R. B. C., mill. per c.mm.	Hgb., %.	Ret. %.
1.5	34	1.3	1.8	52	0.8	2.1	59	5.0	1.6	46	1.5	1.5	44	1.2
1.5	40	1.6	1.8	51	1.2	1.8	55	5.3	1.4	44	1.7	1.5	43	0.8
1.5	35	1.0	1.7	49	0.6	2.0	57	4.5	...	..	0.8	1.6	43	1.8
1.2	32	...	1.6	43	1.6	...	..	4.2	1.6	46	0.1	1.5	44	0.3
...	..	0.6	...	..	0.8	2.0	57	5.0	1.6	45	0.5	1.6	43	0.2
1.2	32	3.1	1.3	45	1.1	2.2	59	4.4	...	..	1.9	1.5	40	0.1
1.4	32	3.8	1.3	53	0.8	2.3	63	4.5	1.4	44	2.4	...	..	1.2
1.7	35	3.1	1.4	49	2.1	2.0	72	4.7	1.5	43	3.8	1.3	42	1.6
1.6	30	3.6	1.4	45	0.5	1.9	69	4.8	1.6	42	4.0	1.4	39	1.1
1.6	35	2.8	1.6	39	1.8	2.5	70	4.1	1.6	43	3.6	1.3	38	1.4
1.5	35	4.0	1.3	..	2.5	...	..	5.0	1.4	43	3.0	1.5	45	1.0
...	..	6.8	...	..	2.7	2.5	69	6.3	1.6	48	3.3	1.5	43	1.4
1.3	37	9.4	1.3	44	5.3	2.4	72	5.4	...	..	...			
1.5	34	9.3	1.2	..	6.7	2.6	76	6.8	1.5	44	1.2			
...	..	14.1	...	..	6.1	...	..	8.3						
1.4	36	9.1	1.3	39	6.1	2.4	75	7.6						
1.4	35	9.0	1.4	38	7.7	2.4	69	6.5						
1.6	31	7.9	1.6	43	5.0	...	..	6.1						
...	..	5.6	...	..	7.0	2.3	83	4.6						
1.6	38	3.6	1.3	39	5.4									
...	..	...	1.6	49	4.4									
"Extralin," 12 capsules.			"Extralin," 12 capsules.			"Extralin," 12 capsules.						"Extralin," 12 capsules.		
1.6	38	3.6	...	..	3.4	2.3	83	4.6	...	..	...	1.5	43	1.4
1.7	37	0.7	...	..	4.0	2.6	81	4.7	...	..	...	1.5	43	1.7
1.8	37	2.8	1.9	52	4.2	2.8	72	4.8	...	..	...	...	..	2.0
1.5	42	0.7	1.6	57	3.2	2.7	75	2.7	...	..	...	1.4	43	2.3
1.5	36	1.0	2.1	54	2.7	2.6	75	2.8	...	..	...	1.7	42	2.1
1.7	44	3.0	2.0	59	2.3	2.6	76	3.6	...	..	...	1.6	46	2.6
...	..	5.8	1.9	59	3.4	...	..	7.6	...	..	...	1.8	46	10.2
1.7	46	10.1	1.8	..	6.4	2.8	76	7.5	...	..	...	1.8	48	18.8
2.1	56	12.2	...	..	7.0	3.0	81	7.5	...	..	...	1.7	50	25.2
2.5	56	10.5	1.9	66	6.9	2.9	77	7.7	...	..	...	...	..	17.8
2.2	60	9.0	2.1	61	7.5	2.9	76	5.2	...	..	...	2.0	50	19.9
2.5	61	4.4	2.2	71	5.2	2.9	73	5.5	...	..	...	2.3	51	19.2
...	..	3.6	2.4	69	5.3	3.1	85	3.6	...	..	...	2.6	55	12.6
...	..	2.0	3.0	72	4.6	...	..	...	...	..	...	2.5	59	10.9
2.5	42	2.0	2.5	71	4.6	...	..	...	...	..	...	2.9	61	9.9
2.4	56	1.8	...	..	4.3	...	..	...	...	..	...	2.9	61	...
3.1	60	0.8	2.6	84	3.3									
3.2	64	1.6	2.8	85										
3.6	67	0.8												

TABLE 2.—RESPONSES OF BLOOD OF PATIENTS HAVING PERNICIOUS ANEMIA TO LIVER EXTRACT-GASTRIC JUICE DIGESTS. GASTRIC JUICE FRACTIONATED BY ONE-HALF SATURATION WITH AMMONIUM SULPHATE.

Case No.	8.			9.			10.			10.			11a.		
Method used in fractionation of gastric juice	One-half saturation with ammonium sulphate			One-half saturation with ammonium sulphate, redissolved, then precipitated with alcohol.			One-half saturation with ammonium sulphate, redissolved, then precipitated with alcohol.						Casein adsorption + one-half saturation of supernatant fluid with ammonium sulphate.		
Fraction of gastric juice used	Precipitate.			Precipitate.			Filtrate.						Precipitate.		
Cc. gastric juice derived from	120 cc.			150 cc.			150 cc.						150 cc.		
Day.	R.B.C., mill. per c.mm.	Hgb., † %	Ret., %	R.B.C., mill. per c.mm.	Hgb., %	Ret., %	R.B.C., mill. per c.mm.	Hgb., %	Ret., %	R.B.C., mill. per c.mm.	Hgb., %	Ret., %	R.B.C., mill. per c.mm.	Hgb., %	Ret., %
..	2.8	61	2.4	1.9	60	3.1	1.4	38	0.5	...	..	...	1.7	51	1.5
1	...	..	3.9	2.2	59	0.6	...	..	0.8	...	..	...	1.9	48	1.3
2	2.4	64	3.2	...	..	3.9	1.3	37	1.4	...	..	...	1.7	50	2.4
3	2.3	64	1.4	1.9	53	3.3	1.2	39	2.8	...	..	...	1.7	53	2.0
4	2.0	61	2.0	2.3	61	0.8	1.6	38	2.3	...	..	...	...	..	1.3
5	2.4	61	4.9	2.3	57	2.4	1.2	38	1.6	...	..	...	2.1	53	10.2
6	2.4	61	7.8	...	..	2.9	1.3	40	2.2	...	..	...	2.1	55	14.8
7	2.5	66	8.5	2.4	60	8.0	...	..	3.4	...	..	...	2.1	59	17.2
8	...	..	14.5	2.1	63	7.8	...	..	3.0	...	..	...	2.5	63	17.7
9	2.7	72	7.2	...	..	7.8	1.5	42	4.2	...	..	...	2.6	63	11.8
10	2.5	67	7.5	2.3	65	6.6	1.4	41	2.4	...	..	...	2.5	69	13.5
11	2.4	61	4.7	2.8	66	6.0	...	..	...	...	..	...	...	..	5.0
12	2.9	69	3.6	2.5	70	5.3	...	..	...	...	..	...	2.7	61	2.9
13	2.7	67	2.2	2.7	69	5.7									
14	3.4	75	3.6												
15	...	..	3.7												
16	3.8	76	3.8												
Daily therapy	"Extralin," 12 capsules.			"Extralin," 12 capsules.			10 gm. whole liver + 80 cc. gastric juice.			"Extralin," 12 capsules.			"Extralin," 12 capsules.		
..	3.8	76	3.8	2.7	69	5.7	1.4	41	2.4	1.6	56	3.4	2.7	61	2.9
1	3.3	71	1.5	3.0	72	4.6	1.2	42	2.7	...		6.0	2.8	67	4.6
2	3.4	71	3.5	2.4	74	2.0	1.1	39	2.9	1.9	53	5.7	3.0	73	4.5
3	3.4	69	2.3	...	..	1.5	1.3	42	3.6	2.1	56	6.8	2.8	67	4.0
4	3.6	71	...	2.6	65	3.0	1.2	40	7.8	1.9	51	6.4	2.8	69	4.8
5	3.5	73	1.8	2.9	74	2.1	...	..	10.8	2.4	58	9.5	3.1	66	4.0
6	...	..	1.2	3.1	76	2.4	1.2	43	12.4	2.5	57	15.1	...	..	3.4
7	3.5	74	2.0	3.1	76	2.2	1.6	46	11.2	2.3	56	9.5	3.0	63	3.1
8	3.3	70	1.4	2.8	70	4.4	1.5	48	11.1	...	..	8.3	3.6	72	2.4
9	3.3	75	2.2	...	..	2.4	1.6	48	7.8	2.4	56	6.6	3.7	78	2.2
10	3.4	73	1.8	...	..	2.6	1.5	49	6.6	2.5	64	5.6	4.0	73	1.8
11	3.4	76	1.4	3.0	76	1.2	1.6	56	3.4	2.8	61	2.6			
12	4.0	82	1.2	3.0	76	...	...	..	...	3.0	65	2.4			
13	...	..	...	3.1	83	1.0	...	..	...	2.8	66	4.6			
14	...	..	...	3.3	75	1.6	...	..	...	2.7	..	2.0			
15	...	..	...	3.6	76	1.2	...	..	...	..	..	4.0			
16	...	..	...	3.7	89	...	...	..	...	3.2	72	2.8			

† Newcomer method.

nium sulphate adsorbed on the casein, as it produced marked nausea when fed to Case 11. There was, however, a maximal reticulocyte response (17.7% on the eighth day with original red blood cell level of 1.70 million). The clinical response and rise in red blood cell count was very satisfactory.

The removal of pepsin and rennin from the gastric juice by precipitation with tricalcium phosphate offered the opportunity to remove these enzymes without adding any extraneous proteins. The tricalcium phosphate was prepared as described by Utkin.[16] It was possible completely to remove all the rennet activity from the gastric juice by this method. However, during the removal of the last traces of this activity much of the intrinsic factor was also removed, although demonstrable amounts still remained. The response of Case 12 (Table 3), who received a liver extract gastric juice digest made with 120 cc. gastric juice from which all but 0.08 to 0.24 mg. of rennin per cc. had been removed, was greater than the response of Case 13. The digest administered to the latter patient was made with 150 cc. of gastric juice completely freed of pepsin and rennin with tricalcium phosphate.

The results obtained using casein and tricalcium phosphate suggested that if the right reagent were used, the enzymes pepsin and rennin might be satisfactorily separated from the intrinsic factor by the process of adsorption. Lloyd's reagent was selected next as a possible reagent. It was found that it was necessary to add from 10 to 15 gm. of the reagent per 100 cc. of gastric juice to completely remove the enzymes pepsin and rennin. When a liver extract gastric juice digest made with 150 cc. of gastric juice so freed from pepsin and rennin was fed daily to Case 14, a maximal reticulocyte response (33.6%) followed. A similar liver extract gastric juice digest made with 100 cc. of this pepsin- and rennin-free gastric juice, when fed for 10 days to Case 15, produced a rise in reticulocytes of only 12.8% and no rise in red blood cell count. When the amount of the pepsin- and rennin-free gastric juice used in the digest was increased to 150 cc., a second rise in reticulocytes up to 38.9% followed. There was a satisfactory rise in the red blood cell count. This response seemed maximal, but when the patient received 6 vials of liver extract per day by mouth and 6 cc. concentrated liver extract twice a week intramuscularly, a third reticulocyte rise (20.6%) was obtained (Table 4).

The intrinsic factor in the gastric juice after removal of all the peptic enzymes by adsorption with Lloyd's reagent was found to be precipitated on saturation with ammonium sulphate (Cases 16*a* and 16*b*), although considerable intrinsic factor was lost by this procedure.

In the preceding studies, unconcentrated gastric juice was treated with Lloyd's reagent; whereas, the gastric juice used in liver extract gastric juice digest fed to Case 11*b* was first concentrated by ultra-

filtration before it was treated with Lloyd's reagent. This procedure greatly reduced the total amount of Lloyd's reagent required to remove the pepsin and rennin. A reticulocyte response of 20.4% was obtained when this digest was fed to Case 11*b*. There, however, was a slight secondary response (6.5%) to a known potent material.

These responses indicated that from one-half to two-thirds of the intrinsic factor was lost during the adsorption of the enzymes pepsin

TABLE 3.—RESPONSE OF THE BLOOD OF PERNICIOUS ANEMIA PATIENTS TO LIVER EXTRACT-GASTRIC JUICE DIGESTS. (THE GASTRIC ENZYMES WERE REMOVED FROM GASTRIC JUICE BY ADSORPTION WITH TRICALCIUM PHOSPHATE.)

Case No.	12.			13.		
Method used in fractionation of gastric juice	Tricalcium phosphate adsorption.			Tricalcium phosphate adsorption.		
Mg. rennin per cc. filtrate	0.08 to 0.24.			0.		
Fraction of gastric juice used	Filtrate.			Filtrate.		
Cc. gastric juice derived from	120 cc.			150 cc.		
Day.	R.B.C., mill. per c.mm.	Hgb.,* %.	Ret., %.	R.B.C., mill. per c.mm.	Hgb.,* %.	Ret., %.
..	2.4	62	0.9	2.0	56	1.4
1	2.4	..	0.6	1.8	50	1.5
2	...	..	0.2	1.6	50	2.6
3	2.2	69	0.4	1.3	50	4.0
4	2.1	68	0.4	1.5	49	4.1
5	2.7	69	1.5	1.8	51	8.9
6	2.3	66	4.1	...	..	11.1
7	2.6	72	5.5	2.0	56	12.5
8	2.5	65	8.5	2.2	58	13.0
9	...	..	5.6	2.2	54	13.6
10	2.5	63	8.4	2.1	53	8.4
11	2.7	69	6.5	2.1	51	5.8
12	3.1	72	5.6	2.0	53	2.8
13	2.0	70	3.1			
Daily therapy	"Extralin," 12 capsules.			"Extralin," 12 capsules.		
..	3.0	70	3.1	2.0	53	2.8
1	2.8	70	2.3	...	..	6.8
2	3.0	70	2.4	2.1	52	5.7
3	...	..	2.4	2.0	56	7.4
4	3.0	72	2.6	2.0	55	9.9
5	2.7	71	1.9	2.2	57	16.5
6	3.0	77	2.2	2.2	55	23.0
7	3.3	86	4.4	2.3	56	22.5
8	3.3	82	4.5	...	..	23.0
9	3.2	80	3.2	2.8	66	15.6
10	...	..	3.5	2.6	63	10.1
11	...	..	...	2.6	66	13.3
12	...	..	...	2.6	66	13.2
13	...	..	...	2.9	67	10.1
14	...	..	...	2.8	69	10.8

* Newcomer method.

TABLE 4.—RESPONSE OF BLOOD TO LIVER EXTRACT-GASTRIC JUICE DIGESTS. (GASTRIC ENZYMES

TABLE 4.—RESPONSE OF BLOOD TO LIVER EXTRACT-GASTRIC JUICE DIGESTS. GASTRIC ENZYMES REMOVED FROM GASTRIC JUICE BY ADSORPTION ON LLOYD'S REAGENT.

Case No.	14.			15.			15.			16a.			16b.			11b.		
Method used in fractionation of gastric juice	Adsorption with Lloyd's reagent.			Adsorption with Lloyd's reagent.			Adsorption with Lloyd's reagent.			Adsorption with Lloyd's reagent and supernatant fluid saturated with ammonium sulphate.			Adsorption with Lloyd's reagent and supernatant fluid saturated with ammonium sulphate.			Concentrated by ultrafiltration and adsorption with Lloyd's reagent.		
Fraction of gastric juice used	Filtrate.			Filtrate.			Filtrate.			Precipitate.			Precipitate.			Filtrate.		
Cc. gastric juice derived from	150 cc.			100 cc.			150 cc.			150 cc.			200 cc.			200 cc.		
Day.	R.B.C., mill. per c.mm.	Hgb.† %	Ret., %	R.B.C., mill. per c.mm.	Hgb., %	Ret., %	R.B.C., mill. per c.mm.	Hgb., %	Ret., %	R.B.C., mill. per c.mm.	Hgb., %	Ret., %	R.B.C., mill. per c.mm.	Hgb., %	Ret., %	R.B.C., mill. per c.mm.	Hgb., %	Ret., %
..	1.4	39	4.2	1.1	29	4.8	1.0	28	5.9	2.4	75	1.8	2.6	81	3.2	1.7	47	0.8
1	1.3	39	2.5	...	..	4.1	1.0	28	9.9	2.3	73	1.9	2.8	84	3.0	1.7	48	1.6
2	1.4	39	1.9	1.0	28	6.5	1.0	28	10.7	2.4	75	2.0	...	..	2.8	1.8	43	1.0
3	...	..	3.7	1.0	28	5.9	...	..	18.7	2.3	76	1.4	2.6	86	2.9	1.8	45	1.5
4	1.4	37	7.2	1.0	28	3.7	0.9	29	19.6	2.4	77	1.9	2.6	89	2.2	1.8	40	1.2
5	1.3	37	14.4	1.0	29	4.9	1.2	32	30.6	...	..	2.1	2.6	86	2.9	...	..	4.4
6	1.5	38	21.7	1.0	26	8.9	...	..	35.4	2.5	79	1.7	2.7	87	3.3	1.7	41	9.2
7	1.4	44	28.4	0.9	25	10.0	1.3	36	38.9	2.5	80	2.1	2.7	87	2.2	1.9	43	12.6
8	1.5	46	27.1	...	..	10.7	1.5	40	31.4	2.6	82	0.3	2.8	86	3.3	2.0	48	15.4
9	1.8	46	33.6	1.0	28	12.8	1.5	42	31.3	2.5	81	4.5	...	..	3.4	2.2	47	20.4
10	...	..	27.5	1.0	26	12.2	...	..	12.5	2.6	81	3.2	3.0	86	3.0	2.1	47	18.1
11	1.9	50	24.4	1.1	29	10.7	1.7	48	8.1	...	..	...	3.1	89	4.2	2.3	53	11.0
12	2.0	50	22.1	1.0	28	5.9	1.8	47	4.5	...	..	...	3.3	89	1.9	...	..	10.7
13	2.3	54	11.2	...	..	...	...	..	...	...	..	...	3.2	89	1.8	2.4	50	7.5
14	...	..	8.6															
Daily therapy	"Extralin," 12 capsules.						Liver extract (oral), 6 vials + liver extract, 6 cc. (intramuscularly).*						Liver extract, 3 vials.			"Extralin," 12 capsules.		
..	...	..	8.6	...	..	...	1.8	47	4.5	...	..	...	3.2	89	1.8	2.4	50	7.5
1	2.4	52	7.4	...	..	...	...	..	5.2	...	..	...	3.3	89	2.1	2.6	52	6.1
2	2.5	55	7.2	...	..	...	1.6	50	4.2	...	..	...	3.2	92	1.8	2.5	52	3.7
3	...	..	3.2	...	..	...	1.8	50	12.8	...	..	...	...	..	1.9	2.6	54	3.7
4	2.6	70	3.7	...	..	...	2.1	50	19.4	...	..	...	3.2	88	2.1	2.7	56	4.8
5	3.0	72	3.8	...	..	...	...	..	20.2	...	..	...	3.5	92	1.5	...	..	3.6
6	3.0	76	3.1	...	..	...	2.1	51	20.6	...	..	...	3.4	89	3.0	...	..	4.0
7	3.3	63	2.3	...	..	...	2.1	50	8.6	...	..	...	3.4	88	3.5	2.7	56	6.1
8	3.3	63	1.8	...	..	...	2.3	53	5.5	...	..	...	3.4	92	2.6	3.0	58	5.6
9	3.1	66	1.5	...	..	...	2.5	57	6.0	...	..	...	3.3	88	2.3	3.1	61	6.5
10	...	..	0.4	...	..	...	2.6	63	4.2	...	..	...	...	..	2.3	3.2	64	3.6
11	3.4	69	2.0	...	..	...	2.9	60	...	...	..	...	3.5	89	1.5			
12	3.3	67	1.6	...	..	...	...	..	...									

* Intramuscular liver extract administered twice weekly.

† Newcomer method.

and rennin by the Lloyd's reagent. However, by this procedure the pepsin and rennin could be completely separated from the intrinsic factor without adding any extraneous proteins. This method, therefore, appears to be quite satisfactory as a preliminary step for the further purification of the intrinsic factor.

It was felt advisable to do a few simple tests on the purified gastric juice at this time, although we realized that the intrinsic factor was far from being in a pure state. The original gastric juice showed titratable acid = 69 cc. N/10 per 100 cc., rennin =

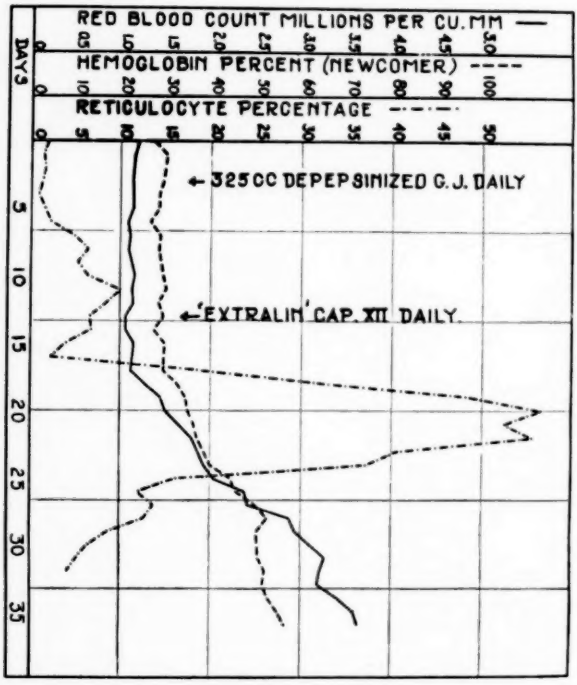
RED BLOOD COUNT MILLIONS PER CU. MM
HEMOGLOBIN PERCENT (NEWCOMER)
RETICULOCYTE PERCENTAGE
DAYS
← 325 CC DEPEPSINIZED G. J. DAILY
← 'EXTRALIN' CAP. XII DAILY.

CHART I

34 mg./cc., mucous sugar = 0.175 mg./cc., and total nitrogen = 0.498 mg./cc. After the treatment of 100 cc. of gastric juice with 100 gm. of Lloyd's reagent, the titratable acid = 15 cc. N/10 per 100 cc., rennin = 0 mg./cc., mucous sugar = 0.0025 mg./cc., and nitrogen = 0.13 mg./cc. (26% of original nitrogen). The original gastric juice showed a strong biuret reaction, heat coagulable proteins, a very strong Molisch test and a weakly positive ninhydrin reaction. Precipitates were formed by 80% alcohol and half saturation with ammonium sulphate. The gastric juice, after adsorption with Lloyd's reagent, showed a questionably positive

biuret reaction, no heat-coagulable proteins, negative Molisch and negative ninhydrin reaction. There were no 80% alcohol or half saturated ammonium sulphate precipitates, although there was a slight but definite saturated ammonium sulphate precipitate, and, as shown above (Cases 16*a* and 16*b*) this precipitate contained the intrinsic factor. It is interesting that the partially purified intrinsic factor has many of the properties of the purified liver extract preparations described by Dakin and West,[4] and Laland and Klem.[11]

Following the completion of these studies, Greenspon[8] reported that pepsin was antagonistic to the antipernicious anemia factor in gastric tissue, as he found that the feeding of normal gastric juice (about 250 cc. daily), peptically inactivated, was effective in pernicious anemia without the addition of beef or other source of "extrinsic factor." We had, however, previously[10c] reported that the feeding alone of 150 cc. of gastric juice from which the enzymes pepsin and rennin had been removed by casein precipitation produced no hematologic response. Greenspon, in explaining Castle's results, concluded that the beef adsorbed the pepsin of the gastric juice and thus protected the antipernicious anemia principle. This explanation cannot apply to the increase in activity of liver extract after incubation with normal human gastric juice, as the peptic activity after incubation was as great as before. It seemed necessary, however, to repeat Greenspon's experiment. The gastric juice was collected daily from 2 normal individuals into flasks surrounded by an ice-salt mixture. It was immediately brought to pH 7.2–7.4 by the addition of strong NaOH and stored in the ice box until it was fed by stomach tube to Case 17 (Chart I) at 4.30 P.M. The average amount the patient received daily was 325 cc. Rennet activity of the juice tested just before administration averaged 4.4 mg./cc. The patient was on a meat-, egg-, and milk-free diet; and received the evening meal at 6.30 P.M. A reticulocyte peak of 10% was reached on the eighth day of treatment, but the red blood cell count showed no increase. The gastric juice in this experiment was not filtered, so the large amount of mucus and small amount of blood present in the unfiltered gastric juice might have supplied a small amount of extrinsic factor thus producing this slight reticulocytosis. This response, however, was far from maximal as a 56.5% reticulocyte rise followed the oral administration of a known potent material (Chart I).

Flood and West,[6] Ungley and Moffett,[15] Hanes, Hansen-Prüss and Edwards,[9] Fitz-Hugh and Creskoff,[5] and Castle and Ham[3] have also reported observations at variance with Greenspon. Castle and Ham, however, concluded that incubation outside of the body of the patients should be eliminated from future studies on intrinsic and extrinsic factors, as in the presence of native pepsin and HCl a portion of the intrinsic factor is lost by this procedure. As all the studies reported here were carried out under the same condi-

tions, the destruction of intrinsic factor by the incubation (2 hours) should not interfere in comparing the activity of the various fractions of the gastric juice.

Summary and Conclusions. The daily oral administration of 325 cc. of "depepsinized" human gastric juice to a patient with pernicious anemia in relapse did not produce a satisfactory response of the blood, thus further emphasizing the need of both an intrinsic and extrinsic factor in hematopoiesis, as postulated by Castle and his associates.

The intrinsic factor in human gastric juice is partially soluble in 80% alcohol and 80% acetone, but it does not dialyze through cellophane, either before or after the precipitation of pepsin and rennin with casein.

One-half saturation with ammonium sulphate precipitates the intrinsic factor from normal human gastric juice and from gastric juice previously freed of pepsin and rennin by casein precipitation. This precipitate containing the intrinsic factor, however, is not soluble in 80% alcohol.

The gastric enzymes, pepsin and rennin, and the gastric mucin can be separated from the intrinsic factor by adsorption of the enzymes and mucin on tricalcium phosphate or Lloyd's reagent.

The intrinsic factor thus obtained is in a relatively pure state and no longer is precipitable on half saturation with ammonium sulphate. The saturated ammonium sulphate precipitate, however, contains the intrinsic factor.

There is considerable loss of intrinsic factor during the process of adsorption of the enzymes with tricalcium phosphate.

The loss of the intrinsic factor on Lloyd's reagent is not excessive and this procedure offers a good method for the further purification of the intrinsic factor.

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THE TREATMENT OF MYASTHENIA GRAVIS.

Report of Six Cases.*

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This report is a summary of the treatment of 6 cases of myasthenia gravis. The diagnosis was made on the history and observation of changing palsies, particularly of the extraocular muscles, and the general increased fatigability. The favorable response to the administration of prostigmin (dimethyl carbamic ester of hydroxyphenyltrimethyl ammonium methylsulphite) also proved to be of diagnostic importance. Each patient was subjected to a number of different forms of treatment in such a way as to provide a control, both in relation to the other members of the group, and to his own basic condition. In this way an attempt was made to arrive at the best therapy for each patient as an individualized problem.

The nature of myasthenia gravis and its position in the classification of diseases remain in doubt. The earliest report of myasthenia gravis of which we are aware is by Willis[9] in "The London Practice of Physick." This description mentions the progress and changeability of symptoms throughout the day, and the predominance of symptoms referable to muscles supplied by the brain stem nuclei. Willis was of the opinion held by many subsequent authors that the condition was, at least in part, hysterical. Buzzard,[4] in 1905, observed collections of lymphocytes in the striated muscles, and the frequent thymic enlargement. He regarded myasthenia gravis as a syndrome resulting from lymphosarcoma of the thymus with metastases to the muscles. Though his *observations* have been confirmed by others, his *interpretation* was not accepted. Norris,[15] from a study of 4 autopsied cases and those in the literature, estimated that at least one-half showed gross thymic involvement. Skinner[19] recorded a case in which there was gross involvement of the thymus and other lymphoid structures such as the spleen and superficial lymph nodes. Rosenow and Heilman[18] regarded the myasthenic syndrome as due to a specific streptococcus. Lymphocytic infiltration though a fairly constant finding in myasthenia gravis may also be found in other diseases[3]; however, it is worthy

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of note that lymphorrhages are not found in the muscular dystrophies.

Metabolic studies have given no clue to the nature and etiology of myasthenia. Boothby and his collaborators[1] found no significant metabolic abnormalities after extensive study of a group of these patients.

The site of the lesion causing this syndrome has been perplexing until recently. It is of clinical importance that the visceral muscles such as the iris and myocardium are frequently affected along with somatic musculature.[14] Microscopic studies of the central nervous system and peripheral nerves have yielded no demonstrable lesions. The muscle tissues are relatively normal histologically, except for the lymphorrhages which are insufficient quantitatively to account for the profound symptomatology. Physiologic study has shown that the efferent nerve conducts normally[13] and that the fatigued myasthenic muscle responds to direct stimulation. This suggests that the obstruction to the passage of impulse from nerve to muscle may exist at the junction of these two structures. Since no anatomic explanation could be offered, a physiologic approach to the problem was attempted. Recently this suspicion has been strengthened by work[13] showing that there is an area at the myoneural junction in myasthenia gravis at which impulses suffer decrement or extinction. While it can be stated with reasonable certainty that the myoneural junction is one site of physiologic disturbance, it is very likely not the only one. The observation that myasthenic symptoms are favorably influenced by ephedrine[6] and, as shown in our case reports, by benzedrine, would indicate that other physiologic sites are implicated.

As a result of the lack of exact knowledge of the nature and seat of the primary lesions in myasthenia gravis many modes of treatment have been attempted. These varied with the concept of the underlying etiology. When the relationship to the muscular dystrophies was deemed important, the aim was to correct some possible metabolic disturbance. When the thymic aspect was stressed, treatment was directed at the thymus. With the new emphasis on the myoneural junction, drugs were employed the pharmacologic activity of which centered about this point. The following is a review of the chief modes of treatment. The results of treatment in our 6 cases are discussed. The occurrence of spontaneous remissions in the course of myasthenia gravis was fully recognized, but the prompt and lasting response to some of the agents make it appear that the relief of symptoms was not in the nature of a remission.

Treatment with Aminoacetic Acid. Remen[17] thought that the metabolic disturbances in creatine-creatinine relationships which have been demonstrated for the myopathies, especially of the atrophic or pseudohypertrophic types, were likewise present in

myasthenia gravis. Aminoacetic acid (glycine, glycocoll, Glykhepar) is indicated theoretically and to a somewhat less extent empirically in the treatment of this creatine-creatinine disturbance in the myopathic dystrophies. Remen concluded, basing his opinion on one case studied, that "Glykhepar should be employed in such (myasthenic) cases." Boothby[2a] tentatively presented a case in which glycine was tried. Others[20] found no benefit resulting after 5 weeks of intensive glycine therapy in myasthenia gravis.

Our own group showed no effect on symptoms with glycine in 15 gram daily doses for periods varying from 2 weeks to 3 months. Glycine was tried in 5 cases, but none showed any symptomatic change.

Physostigmine and its Analogues. In 1895 Jolly[10] suggested the use of physostigmine in myasthenia, but noted that its usefulness was restricted by untoward side-reactions, such as diarrhea, excessive perspiration, and so forth. Walker[23] suggested that myasthenia gravis symptomatically resembled curare poisoning. Curare paralyzes the muscles by its action on the myoneural junction and physostigmine is its pharmacologic antagonist in this action. She found that physostigmine (and later prostigmin) had a distinctly beneficial effect on the symptoms of myasthenia. This observation has been amply confirmed by others.[11,16,22] Everts[7] found the oral administration of prostigmin satisfactory. Viets and Schwab[21] suggest that the action of prostigmin in myasthenia gravis is diagnostic of that condition (a suggestion with which we are in entire accord). The following 2 brief case reports demonstrate the value of the prostigmin test in distinguishing cases which resemble myasthenia gravis:

Case Abstracts. C. A., a white man of 70, complained of difficulty in seeing. On examination he showed bilateral lid ptosis and bilateral complete external ophthalmoplegia. Both pupils were dilated and reacted poorly to light. His symptoms and signs were at a minimum in the morning and progressed as the day advanced. He showed no reaction to the administration of prostigmin in sufficient dosage for 1 week. We concluded that his was not a case of myasthenia gravis and, in the absence of lues, the diagnosis of multiple lesions of vascular origin in the midbrain was made.

Another case, L. H., a 47-year-old married woman, had *changing* extraocular palsies and difficulty with articulation and deglutition over a period of 4 years and did not respond to intramuscular or oral administration of prostigmin. Spinal fluid studies later established the diagnosis of neurosyphilis.

All of our cases were strikingly benefited by the use of prostigmin. The improvement was noted subjectively and objectively by a return to the normal state of the functions of the extraocular muscles. When the drug was withheld there was an immediate lapse toward the former state. Prostigmin was given orally and the dose individually adjusted. Each dose produced an effect lasting 1 to 4 hours. No development of tolerance to the drug has been observed,

i. e., one 15-mg. tablet is as effective after several months of prostigmin administration as at the beginning. All 6 patients finally arrived at approximately the same dosage, namely 5 to 9 15-mg. tablets evenly spaced throughout the waking day. All patients showed a weight gain varying from 5 to 25 pounds and had excellent appetites. Occasional diarrheas were controlled easily with tablets of atropine sulphate, gr. $\frac{1}{150}$, taken orally when necessary. One of our cases prior to treatment showed evidence of a marked myasthenic reaction of the myocardium which was controlled by prostigmin. The myasthenic pupillary reaction to sustained light stimulation was abolished by prostigmin. None of our cases shows a *complete* remission of symptoms, but the dose is limited by the expense of the drug and its tendency in higher quantities to produce diarrhea and sweating.

Potassium Chloride. Dale, Feldberg and Vogt[5] demonstrated that on repeated stimulation of an efferent nerve acetylcholine is produced at the myoneural junction, except when the muscle is exhausted. Feldberg and Guimarais[8] showed that the administration of potassium chloride stimulates the production of acetylcholine in the structures where acetylcholine is normally produced. Function of the myoneural junction is presumed to be dependent upon the availability of acetylcholine at the junction. On the basis of these data potassium chloride has been given by mouth. Laurent and Walther[12] thought their cases were helped by potassium chloride and arrived at the conclusion that small repeated doses aid in the action of prostigmin. Wade[22] finds no effects from potassium chloride.

Our series of patients showed no improvement with the use of potassium chloride either alone or as an adjuvant to some other form of treatment.

Sympathomimetic Drugs. Dr. Harriet Edgeworth, suffering from myasthenia gravis, accidentally discovered that ephedrine gave her considerable relief.[6] Boothby[2b] reported that 10 of 12 patients were benefited by the use of ephedrine.

Four of our 5 cases showed slight but definite improvement with ephedrine capsules, gr. $\frac{3}{8}$, taken 2 to 4 times a day. A certain unpleasant tremulousness detracted from these benefits. An attempt to find a satisfactory adjuvant to prostigmin which would be free of the undesirable effects of ephedrine led to the employment of benzedrine in the series of cases presented here. Two of the 5 cases received prostigmin alone. The other 3 received benzedrine and prostigmin and showed marked improvement. These last 3 then were treated with benzedrine alone and in only one of these was the improvement sufficient to warrant the further omission of prostigmin. In this case (No. 3), however, the continued use of benzedrine produced insomnia. It was found that a satisfactory compromise could be ensured by restricting the use of benzedrine to the early

part of the day, and then switching to prostigmin. A tendency toward wakefulness was the sole ill effect brought about by the use of benzedrine. We believe that the sympathomimetic drugs are useful as adjuvants to prostigmin in the treatment of myasthenia gravis.

Roentgen Therapy to the Thymus. Through the courtesy of Dr. Karl Kornblum and his staff all of our patients were studied roentgenographically for enlargement of the thymus, but no evidence of such enlargement was found. Nevertheless, 3 patients were given Roentgen therapy directed to the thymus, 800 r. through each of two ports. The symptoms of these 3 patients after such therapy did not show any significant change from the pretherapeutic state or from the 2 patients kept as controls.

The following is a brief summary of the 6 cases:

Case Abstracts. CASE 1.—M. B., female, aged 20, since April, 1936, has had ptosis and double vision, some difficulty with phonation and chewing, and generalized weakness. On examination there were ptoses of both upper lids, a myasthenic pupillary reaction, tachycardia, and dissociated extraocular palsies. The muscular symptoms became progressively worse as the day wore on. A hypodermic injection of one ampule of prostigmin (brown label) caused all these signs and symptoms to disappear within 3 minutes. Studies at the Graduate Hospital showed no roentgenologic evidence of enlargement of the thymus and no laboratory evidence of disturbance in blood urea nitrogen, blood calcium and phosphorus, blood urea creatine and creatinine and basal metabolic rating.

Treatment. The patient was given 15 gm. glycine every day for 6 weeks with no effect. A daily dose of 30 gm. of potassium chloride over a period of 10 days produced no change, 1600 r. of irradiation of the thymus had no effect. Ephedrine sulphate, gr. ¾ t.i.d., caused a slight improvement, but made the patient "jittery," 100 mg. mecholyl hypodermically, produced marked vagal symptoms but no amelioration of the muscular signs. Marked benefit was obtained from the oral administration of prostigmin. The average daily dose was 5 to 7 of the 15-mg. tablets. From the patient's point of view, her well-being was increased by the addition to prostigmin of 10 mg. of benzedrine twice daily. The addition of lactose tablets, identical in appearance with the benzedrine tablets, to the daily prostigmin régime had no such beneficial effect. The cardiac rate is easily controlled by the prostigmin therapy.

CASE 2.—J. B., male, aged 46, developed bilateral ptosis in 1906. A gradual progression of the symptoms ensued to the present. His condition became worse in 1918 when the patient suffered an attack of influenza. The myasthenic symptoms were minimal in the morning and increased with fatigue. Double vision, dysphagia and generalized weakness were prominent. On examination there were bilateral lid ptoses, almost complete extraocular palsy, and bilateral facial weakness of peripheral type.

Treatment. Administration of glycine, 15 gm. daily for 2 weeks, produced no change. Potassium chloride, 20 gm. daily for 1 week, exhibited a similar lack of response. Irradiation of the thymus caused no improvement. Prostigmin tablets, 5 to 8 daily, produced such marked symptomatic benefit that the patient was able to obtain a job as laborer. Ten milligrams of benzedrine in divided doses intensified the action of the prostigmin. The highest expedient dose of prostigmin failed to lift the lids completely off the pupil. A surgical operation was performed to raise the right lid and up

to the time of writing (3 months postoperative) no severe corneal complication has been observed.

CASE 3.—E. W., female, aged 39, first noticed ptosis of the left lid when reading and at night in July, 1936. Later diplopia and generalized weakness appeared. No bulbar symptoms occurred. The first examination revealed no abnormalities. At subsequent examinations ptosis and extraocular palsies were found.

Treatment. Glycine, 15 gm. daily, was used over a period of 2½ months with no benefit to the patient. Potassium chloride, 30 gm. daily, gave no relief. Ephedrine, gr. ¾ twice daily, caused some improvement which was not noted with blank controls. Slightly better results were obtained from benzedrine, 10 mg. twice a day. Marked amelioration of symptoms was noted with prostigmin tablets, 5 to 8 per day. This patient experienced greater subjective and objective relief when a combination of prostigmin and benzedrine was used. Later the administration of 3 10-mg. benzedrine tablets alone gave best results.

CASE 4.—M. H., female, aged 23, developed in June, 1936, diplopia, speech difficulties and dysphagia. These symptoms were least incapacitating in the morning and were intensified as the day progressed. Subsequently generalized weakness and lid ptosis were noticed. Examination at various times revealed lid ptosis, changing extraocular palsies and a myasthenic pupillary reaction.

Treatment. Glycine, 15 gm. per day, was given for 1 week with no change. Potassium chloride in a daily dose of 30 gm. for 3 days produced no results. Prostigmin, 6 to 8 tablets a day, was employed with marked benefit. As an adjuvant, benzedrine has been very helpful.

CASE 5.—H. G., male, aged 35, developed in 1935 bilateral ptosis and generalized weakness. Examination in 1936 revealed bilateral ptosis and changing extraocular palsies. There was bilateral seventh nerve weakness of the peripheral type.

Treatment. Glycine, 15 gm. per day for 1 week, produced no improvement. Potassium chloride, 30 gm. daily for 1 week, evoked no response. Ephedrine and benzedrine had no effect whatsoever on this patient's symptoms. Prostigmin, 5 to 6 tablets daily, permit him to work as a laborer.

CASE 6.—L. B., a man of 61, 5 years ago complained of double vision and ptosis. These symptoms became worse as time progressed and, in addition, speech difficulties and generalized weakness became evident. He had been given large doses of glycine and vaccine therapy, but his symptoms were unrelieved. Examination revealed extraocular palsies, a myasthenic pupillary reaction, bilateral ptosis and facial palsies and soft palatal weakness. The cardiac rate was 160 and the blood pressure 190/95.

Treatment. This patient felt stronger and was able to raise both upper lids uncovering the pupils when 1 tablet of prostigmin was given every 1½ to 2 hours. As an adjuvant, benzedrine was given in 2 10-mg. doses daily. The blood pressure at present is 120/80 and the pulse rate 80 to 90. The patient is now able to pursue a routine which is almost normal.

Summary. From a review of the literature it would appear that myasthenia gravis is a disease in which there is a disturbance of the normal passage of impulse from nerve to muscle. The obstruction is probably at the myoneural junction and hypothetically may involve a faulty metabolism of acetylcholine. There may be other factors in the etiology of myasthenia gravis which have not yet been established.

Based on our limited knowledge of the cause of this disease, prostigmin is the therapeutic agent of choice. It has proved valu-

able in the treatment of all of the 6 cases reported. This therapeutic reliability has proved so dependable that the response to prostigmin has come to be employed as a diagnostic procedure. Failure of a case of suspected myasthenia gravis to respond to prostigmin casts doubt on the diagnosis. All of the 6 cases reported here gave a prompt response to prostigmin therapy, while 2 other cases with suspicious symptoms, which did not respond to the drug, were later found to have organic disease of the central nervous system. Based on the experience of others with ephedrine, benzedrine was employed so far as we know for the first time, and found advantageous in 3 of the 5 cases. The use of aminoacetic acid, potassium chloride, and Roentgen therapy produced no beneficial results.

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BOOK REVIEWS AND NOTICES.

THE MEDICAL CLINICS OF NORTH AMERICA, Vol. 21, No. 2 (Boston Number —March, 1937). Pp. 642; illustrated. Philadelphia: W. B. Saunders Company, 1937.

THE 7-paper symposium on blood dyscrasias will undoubtedly attract major attention in this volume. The pedagogic method used in Dr. Hunter's "clinic" on the leukemias seems admirably adapted to the situation, though one must note with regret his contribution to the misuse of "quite." It is pleasant to note that Jackson uses the non-committal term, "Hodgkin's Disease," for that condition, rather than such confusing and unjustifiable terms as "lymphadenoma," "lymphoblastoma," "lymphogranuloma." One wonders who slipped in ascribing Otto's description of hemophilia to 1893, and why no mention of the pathology of hemophilia is made, even in a clinical journal, is a general discourse, such as this is. In the discussion of chlorosis, the nature of the condition must be inferred by the reader; one wishes that it had been stated. With considerable emphasis on treatment throughout, this number maintains the tradition and standard of this excellent publication. E. K.

YOGA: A SCIENTIFIC EVALUATION. By KOVOOR T. BEHANAN, PH.D., Institute of Human Relations, Yale University. Pp. 270; 18 illustrations. New York: The Macmillan Company, 1937. Price, $2.50.

THE venerable Yoga system embraces a series of postural, breathing and psychological exercises for the attainment of discipline; likewise, there is a spiritual content for those wishing to seek salvation through adherence to its complete discipline.

Its philosophic and scientific aspects are here critically interpreted by a native of India who, after being graduated with distinction from Calcutta University, studied philosophy at the University of Toronto and finally received his degree in Philosophy from Yale University. Being determined to make a scientific study of Yoga, this Hindu returned to his native country where he became an earnest student in the institute founded and conducted by the renowned Yogin, Swami Kuvalayananda. After two years, Behanan was again at Yale, this time to subject himself to a series of physiologic and psychologic experiments, the results of which are given in some detail. By reason of these exercises, Behanan attained to an emotional stability and balance not previously known to him, but he adds that the discipline in no way influenced his intellectual outlook. William James, a deep student of mental regeneration, is quoted as having written enthusiastically of the system; to him it seemed that deeper and deeper levels of moral and intellectual power were awakened. Hypnotic phenomena are unlike the mental modifications of Yoga, since the Yogin has a definite recollection of his trance experiences which are so blissful that he longs for their repetition. One learns from Yoga that in its earlier phases, certain similarities to psychoanalysis are shown, but there are definite dissimilarities: Freud is a consistent materialist, "a hard-boiled one," and he and his disciples are too one-sided and dogmatic. Freud's "depth-psychology" would not be considered deep enough by Yoga. The rapid or violent movements known in Western exercises, are against the tradition of this system; certain postures are taken and these may be held from a few minutes to a half hour; the

chapter on postures is elucidated by many excellent illustrations. There is an indispensable glossary and a most complete index. Physiologists, psychologists and psychiatrists cannot afford to neglect this scientific evaluation of Yoga. N. Y.

THE OPERATIONS OF SURGERY. VOL. II. THE ABDOMEN. By R. P. ROWLANDS, M.S. (LOND.), F.R.C.S. (ENG.), Late Surgeon to Guy's Hospital; Late Lecturer on Surgery to the Medical School, and PHILIP TURNER, B.Sc., M.S. (LOND.), F.R.C.S. (ENG.), Consulting Surgeon to Guy's Hospital; Formerly Lecturer on Surgery and Teacher of Operative Surgery to the Medical School. Pp. 1010; 514 illustrations (4 in color). Eighth Edition. Baltimore: William Wood & Co,. 1937. Price, $10.00.

THE second volume of this well-known operative surgery is concerned with operations on the abdomen and the material is presented in much the same manner as in the former editions. The text is up to date and recent literature is generously cited. Statistical tables giving the results of operations are included to provide the reader with the end results of many of the operations described. In some chapters the authors include a discussion of the commoner complications which may follow the operative procedure and they discuss methods of recognizing and avoiding them. The symptoms of the surgical lesion, the indications for operation, the preparation for operation and even the anesthesia are given in orderly fashion, with occasional illustrative cases.

The book includes not only the operations of general surgery, but also those of the urinary tract and of the female pelvic organs. At the end is appended a chapter on surgery of the lumbar sympathetics, and also some notes on the ligation of large vessels. A final chapter on some recent developments contains paragraphs on miscellaneous subjects culled from the literature of interest to the operating surgeon.

In evaluating the book, the reader is impressed by its concise and clear text, its simple yet adequate illustrations. This edition bears out the high standard of previous editions of this work. It is probably one of the best two-volume texts on operative surgery in the English language.

L. F.

MEDICAL UROLOGY. By IRVIN S. KOLL, B.S., M.D., F.A.C.S., Attending Urologist, Michael Reese Hospital. Pp. 431; 92 illustrations and 6 colored plates. St. Louis: The C. V. Mosby Company, 1937. Price, $5.00.

A 400 page book divided into five parts and 42 chapters, touching lightly on almost every phase of Urology, so that its reading is more of a bird's-eye view of the subject, than a book for reference. It is easy and pleasant reading, with many lengthy quotations from selected authorities. The illustrations are well chosen and reproduced. There is good advice on hematuria and pyuria, on the neglected field of endoscopy, and emphasis on when to consult a specialist. A. R.

THE SPECTACLE OF A MAN. By JOHN COIGNARD. Pp. 252. New York: William Morrow & Co., Inc., 1937. Price $2.50.

THIS story, partly fact and partly fancy, is told under a pseudonym by a physician who for years has practised psychoanalysis. Harvesting, a young man with a pronounced mother fixation, met a divorcée; soon they went into executive session which became their habit. At the solicitation of a woman

of easy virtue, they went to her apartment where there was a solitary contact. After some time Harvesting became acquainted with a young lady who neither made nor accepted improper advances and the book ends with their mutual affections deepening. In the meantime, by reason of warring complexes engendered in the unconscious, Harvesting sought help of the analyst to whom his innermost thoughts, actions and dreams were revealed; there is no mincing of words. Four women influenced his life—two sexually. After many analytical months, he was tranquil and emotionally stable. One wonders if women may not have contributed the more to Harvesting's adjustment and adult understanding. N. Y.

HANDBOOK OF MICROSCOPICAL TECHNIQUE. For Workers in Animal and Plant Tissues. Edited by C. E. MCCLUNG, PH.D., Professor of Zoölogy and Director, Zoölogical Laboratory, University of Pennsylvania. Thirty-four Contributors. Pp. 698; 82 illustrations. New York: Paul B. Hoeber, Inc., 1937. Price, $8.00.

THE general arrangement of the subject matter of this book is the same as in the first edition, but many chapters have been revised and enlarged. The list of contributors to this edition has been increased by 10 new names. Among additions to the book are sections on the dioxane method; on microinjection and micromanipulation; on newer hematologic and neurohistologic technique; on the fused quartz rod for illuminating living tissue; on the centrifuge microscope and on fluorescent microscopy. The book is increased by some 200 pages, the paper is of better quality than that of the first edition; the type is more easily read, and the illustrations are clearer. To quote from the review of the first edition that was published in this journal (**177**, 861, 1929) "It is difficult to see how it can be omitted from the bookshelf of any biological laboratory or student earnestly connected with these subjects." H. R.

WHY WE DO IT. An Elementary Discussion of Human Conduct and Related Physiology. By EDWARD C. MASON, M.D., PH.D., F.A.C.P., Professor of Physiology, University of Oklahoma School of Medicine, Oklahoma City. Pp. 177; 5 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, $1.50.

IN this little volume, designed for parents and teachers, more than two pages are given to classification of the psychoses. Of endocrines it is stated, "they greatly modify and they may completely control psychic function and development." Comparatively, there are more than 9 times as many murders here as in England, yet Englishmen's glands are just like ours. The attempt to cover much territory leaves relevant subjects without proper consideration. N. Y.

DIABETES. A MODERN MANUAL. By ANTHONY M. SINDONI, JR., M.D., Chief of the Diseases of Metabolism at the St. Agnes Hospital; Chief Consultant in the Diseases of Metabolism at the Oncologic Hospital, etc. Pp. 240. New York: McGraw-Hill Book Company, Inc., 1937. Price, $2.00.

WITH the increased use of diabetic manuals by patients, physicians are steadily improving the presentation of this type of therapeutic education. Dr. Sindoni's book illustrates this trend. The Reviewer agrees with the laudatory foreword and regards this manual as one of the best that has been produced. F. L.

AUTOPSY DIAGNOSIS AND TECHNIQUE. A Manual for Medical Students, Practitioners, Pathologists and Coroners' Physicians. By OTTO SAPHIR, M.D., Chairman, Nelson Morris Institute for Medical Research; Pathologist, Michael Reese Hospital; Associate Professor of Pathology, University of Illinois Medical School, Chicago. Foreword by LUDVIG HEKTOEN, M.D. Pp. 342; 65 illustrations. New York: Paul B. Hoeber, Inc., 1937. Price, $5.00.

THIS outline of autopsy technique and diagnosis of the lesions seen at autopsy is not at all intended to replace the textbook of pathology, but rather to aid the medical student, the intern on laboratory service and the general practitioner forced by circumstance to perform an autopsy. It describes a modified Rokitansky technique, using either a Y or straight line body incision and removes the organs *en masse*. The valuable information to be obtained from external inspection is stressed and useful tables are adjoined. The heart is opened while still attached to the lungs. Medicolegal aspects are included; its 4 pages on sudden death will be a helpful guide to many. Following a statement as to the order of examination, anatomical details are given about the relations of each organ and then notes about the lesions that one may find in it. Histologic details are purposely omitted. This authoritative statement, in the words of Hektoen's Foreword, "tells competently how to make autopsies and how to study their revelations." E. K.

THE CHEMISTRY OF NATURAL PRODUCTS RELATED TO PHENANTHRENE. By L. F. FIESER, Associate Professor of Chemistry, Harvard University. Pp. 456. Second edition, with an appendix. New York: Reinhold Publishing Corporation, 1937. Price, $7.00.

THE first edition of this excellent monograph on the chemistry and biological significance of sterol compounds was reviewed and highly recommended in this Journal (**192**, 713, 1936). The edition was quickly exhausted. In the meantime, research in the field, which embraces the antirachitic vitamins, bile acids, sex hormones, cardiac stimulants and carcinogenic compounds, has continued at a most rapid pace.

Since the details of structural chemistry are still far from settled, it appeared to Dr. Fieser unwise for the present to revise the material so well presented in the first edition. On the other hand, during the year 1936, some 300 papers of interest in phenanthrene chemistry were published. This newer work is adequately discussed in an appendix of some 90 pages, which is included in the new edition. The index, of course, has been revised appropriately.

The appendix and revised index may be purchased separately for $1.00. This is an excellent idea for the accommodation of the readers who have purchased the first edition. As before, the Reviewer has only the highest praise for this work. D. D.

THE AVITAMINOSES. The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases. By WALTER H. EDDY, PH.D., Professor of Physiological Chemistry, Teachers College, Columbia University, and GILBERT DALLDORF, M.D., Pathologist to the Grasslands and Northern Westchester Hospitals, Westchester County, N. Y. Pp. 338; 3 illustrations and 27 plates. Baltimore: The Williams & Wilkins Company, 1937. Price, $4.50.

THIS book which is directly derived from an earlier work of the senior author is, as its authors describe it, "a helpful manual rather than a complete treatise." The material is well arranged and each vitamin is discussed from

the point of view of its nature, its functions, the clinical and anatomical manifestations and the subclinical forms of its deficiency. Chapters have been added on the vitamins and resistance to infection, and to blood regeneration. Dental caries as a problem of nutrition is also discussed. A section is devoted to methods of bio-assay of the vitamins, clinical tests for vitamin deficiency and tables of vitamin values of foods. E. W.

PRACTICAL EXAMINATION OF PERSONALITY AND BEHAVIOR DISORDERS. By KENNETH E. APPEL, M.D., PH.D., SC.D., and EDWARD A. STRECKER, M.D., A.M., SC.D. Pp. 219. New York: The Macmillan Company, 1936. Price, $2.00.

IN the field of medicine and surgery for sometime there have existed handbooks and short guides for the purpose of aiding students and similar workers in these various fields. In the field of psychiatry—considered by many to be nebulous—there has been a definite need for a similar handbook. Gathered together in this publication one finds a very complete organization of outlines, formal methods of approach, systems of examinations and other aids that will be of practical use to a beginner and to workers in associated fields. It brings the psychiatric field into focus with the general field of medicine in which it belongs. The authors do not pretend that this compilation makes clear the fundamental aspects of patients' disorders. Their intention seems definitely clear that it should be used for practical reference work in the student's early psychiatric life. A broad understanding of the various aspects of the field as a whole is obviously necessary to give early workers a fundamental basis from where they can carry further work into the specialized branch of psychiatry.

Ideally the book should be used in conjunction with supervised teaching rather than independently by the individual student. As indicated by the subtitle it includes many examination methods useful for study of psychiatric disorders in children. If the book is used by workers with an eye to accurate investigation and observation, it will be found to be a valuable tool. L. S.

DAS HORMON DES CORPUS LUTEUM (Biologie, Chemie und Klinik). By DR. ERICH FELS, Dozent für Geburtshilfe und Gynäkologie, Leiter der Abteilung für Biologie und experimentelle Chirurgie am Instituto de Maternidad de la Sociedad de Beneficencia, Buenos Aires. Pp. 169; 40 illustrations. Leipzig: Franz Deuticke, 1937. Price, Paper, M. 12; Bound, M. 14.40.

THIS is a systematically arranged review of the recent literature on the hormone of the corpus luteum, dealing with biological, chemical, and clinical aspects. The author's own investigations are briefly stated. Many good photographs illustrate tissue reactions, and a number of charts and tables illustrate data discussed. I. Z.

DIAGNOSIS AND NON-OPERATIVE TREATMENT OF THE DISEASES OF THE COLON AND RECTUM. By GOTTWALD SCHWARZ, M.D., Professor, University of Vienna; Head, *X*-ray Department, Kaiserin Elizabeth Hospital, Vienna, JACQUES GOLDBERGER, M.D., Consulting Physician, Carlsbad, and CHARLES CROCKER, M.D., New York, N. Y. Pp. 540; 246 illustrations and 9 colored plates. New York: Paul B. Hoeber, Inc., 1937. Price, $10.50.

THE volume begins with excellent and well illustrated discussions of anatomy and physiology of the large bowel. Then comes a large section on the examination of the colon. In discussing proctosigmoidoscopy, the authors describe the commoner instruments and then present their own

"Deplicoptic" proctosigmoidoscope in considerable detail. This instrument has an especially designed optical system somewhat similar to a cystoscope. The tube used is small but a considerable range of vision is permitted by magnification. In the chapter on the examination of feces, the common parasites are described and illustrated. Dr. Schwarz has inserted a long section on the diagnosis of lesions of the large gut by Roentgen ray. Excellent cuts of Roentgen ray films are presented illustrating practically all of the usual and many of the rarer lesions of the colon. Individual diseases of the colon are then discussed in detail, pointing out in each case the etiology, morbid anatomy, symptomatology, diagnosis, findings on proctosigmoidoscopy and, finally, the prognosis and treatment. Diets, drugs and doses are given in detail.

The illustrations throughout the book are well produced. There are 9 pages of colored plates in which an attempt has been made to reproduce the typical proctoscopic findings in various types of colon disease. Although the plates are excellent, one would still be somewhat at a loss to make a diagnosis with no other help than these colored drawings. At the end is appended a list of references concerning the large bowel.

This monograph is an excellent addition to the literature on diseases of the colon and rectum. The authors have studiously avoided any reference to surgical treatment and have confined their efforts to diagnosis and nonsurgical therapy. It should become a part of the library of all those interested in gastro-enterology and proctology. L. F.

CHRISTIAN R. HOLMES. MAN AND PHYSICIAN. By MARTIN FISCHER. Pp. 233; illustrated. Springfield, Ill.: Charles C Thomas, 1937. Price, $4.00.

THIS is chiefly and ostensibly the story of a vigorous, successful personality told in a piquant, unconventional manner that seldom loses clearness thereby. Equally as important is the epic of the attempts to wrest an adequate general hospital for a great city from the fangs of politics and to develop the best possible medical school for his university. E. K.

THE MORPHINE HABIT. Its Painless Treatment. By G. LAUGHTON SCOTT, M.R.C.S., B.A. (OXON), Late Senior Physician, London Neurologieal Clinic; Late Chief Assistant, Neurological Department, Guy's Hospital. Pp. 105; Second edition. London: H. K. Lewis & Co., Ltd., 1937. Price 5s.

WHEN habitually used, morphine causes vagal tone dominance over that of the sympathetic, which condition must be retained during the slow withdrawal; to accomplish this a gradually developed, delirium-free belladonna tolerance is induced, and thereby is offered a physiological basis for the method. Doubtless the permanent value of the treatment is greatly enhanced by the scrupulous care given during convalescence. Many case reports are included but one regrets that the more extensive of these are of physicians. N. Y.

SOURCE BOOK OF ORTHOPÆDICS. By EDGAR M. BICK, M.A., M.D., Adjunct Orthopædic Surgeon, Hospital for Joint Diseases and Mt. Sinai Hospital; Attending Orthopædic Surgeon, Lutheran Hospital, etc. Pp. 376. Baltimore: The Williams & Wilkins Company, 1937. Price, $4.00.

THIS book is an expansion of the author's similar book, issued in photographic format in 1933. (Reviewed in this Journal, **187**, 126, 1934). It is not, as its title indicates, a reprint of important excerpts of contributions that mark the progress of orthopedics; but rather an attempt, in the words

of the Preface, at "a comprehensive history of orthopædic surgery from ancient times to the present day." Even the statement that its object is also to present the source material of contemporary practice requires interpretation, as what is really offered is a correlation by the author of the development of orthopedic practice with basic medical discoveries and with "everchanging social concepts." The first quarter of the book (5 chapters) treats earlier periods chronologically. The rest of the text takes up to the Modern Period, which is here regarded as beginning with the 19th century, though some sections are perforce confined to the 20th century. After six chapters in this section, devoted to Physiology, Pathology, Surgery of Bones, Joints, Muscles, Tendons and non-operative Orthopedics. The book concludes with a chapter on the rise of orthopedic institutions and an Appendix of Orthopedic periodicals. We regret to record our opinion that the book is more "a catalogue of ships" than an entertainingly woven narrative. It could of course still be valuable as an assemblage of historical facts, which with the aid of a full subject index would make it a useful reference book. Unfortunately, however, the subject index is not full, and careless minor errors are so frequent (for instance, 11 on p. 354) that great reliance can hardly be placed on the accuracy of the text in general. The generous references at the end of each section to original and secondary sources of information constitute the book's most valuable feature.

E. K.

SYNOPSIS OF PEDIATRICS. By JOHN ZAHORSKY, A.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine. Assisted by T. S. ZAHORSKY, B.S., M.D., Instructor in Pediatrics, St. Louis University School of Medicine. Pp. 367; 80 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, $4.00.

THIS is an adequate presentation of Pediatrics according to the method developed in the old Quiz Compends. For some students and in some schools such a book might be used as an outline of the course to be amplified by the practical work and clinical lectures. The present edition has been thoroughly revised in many sections and the information brought up to date. The illustrations and plates are accurate and faithful reproductions of the conditions represented. Sections on the rarer syndromes are presented briefly in order to remove emphasis, whereas some sections on the important diseases and fundamental principles have been extended in a comprehensive way.

E. T., JR.

HEMOPHILIA. Clinical and Genetic Aspects. (Illinois Medical and Dental Monographs, Vol. 1, No. 4.) By CARROLL LA FLEUR BIRCH, M.D., Assistant Professor of Medicine. Pp. 151; 23 plates of illustrations, 11 figures, 3 tables and 75 charts. Urbana, Ill.: University of Illinois, 1937. Price, Paper, $2.00; Cloth, $2.50.

THIS monograph is a carefully prepared analysis of 107 hemophilic clinical histories and genealogic trees from verified data collected by the author during 9 years at the Research and Educational Hospital of the University of Illinois. As a first hand study, it is a desirable supplement to the exhaustive compilations by Bulloch and Fildes in 1911, and by Schloessmann in 1930. This monograph will be welcomed by all students of hemophilia; especially noteworthy are the excellent, well-selected photographs of patients.

E. K.

TWINS. A Study of Heredity and Environment. By HORATIO H. NEWMAN, FRANK N. FREEMAN, KARL J. HOLZINGER. Pp. 369; 33 figures, 39 plates of illustrations, and 96 tables. Chicago: University of Chicago Press, 1937. Price, $4.00.

THE contents of this book is made up of studies and observations by a biologist, a psychologist and a statistician, upon 100 pairs of twins.

The method was first to separate these twins into two groups: "identical" ("monozygous," "monochorionic," "uniovular") and "fraternal," of each of which there were 50 pairs. Second, to divide the "identical" twins into two groups: *a*, those that had grown up together, of which there were 30 pairs; and, *b*, those that had been separated in childhood and grown up under different environmental conditions, of which there were 20 pairs.

The twins were then compared with one another and the different groups with one another, using for the purpose the usual physical observations and measurements, and judging the intelligence and personality by the Stanford Revision of the Binet-Simon Test of Intelligence, the Otis Self-administered Test of Mental Ability, Stanford Achievement Test, the Downey Will-Temperament Test, the Woodworth-Mathews Questionnaire and the Tapping tests for objective determination of handedness.

After the elaborate studies were completed it was disappointing to record that no positive conclusions upon the main problem could be arrived at. It seemed that environment played a rôle in the development of personality of identical twins separated in infancy; but the questions involved in comparing the influence of inheritance and environment on intellectual and personal development were too complicated to be settled. The authors think that they have "traced out a few threads in the tangled organism we call man." J. McF.

THE 1936 YEAR BOOK OF GENERAL MEDICINE. Edited by GEORGE F. DICK, M.D., LAWRASON BROWN, M.D., GEORGE R. MINOT, M.D., S.D., F.R.C.P. (HON.) EDIN., WILLIAM B. CASTLE, M.D., A.M., M.D. (HON.) UTRECHT, WILLIAM D. STROUD, M.D., and GEORGE B. EUSTERMAN, M.D. Pp. 848; 178 illustrations. Chicago: The Year Book Publishers, Inc., 1936. Price, $3.00.

ONE of 9 such Year Books, this volume on General Medicine gives adequate surveys of several hundred articles grouped together under the general headings of Infectious Diseases (George F. Dick); Diseases of the Chest (Excepting the Heart) (Lawrason Brown); Diseases of the Blood and Blood-forming Organs; Diseases of the Kidney (George R. Minot) and (William B. Castle); Diseases of the Heart and Blood Vessels (William D. Stroud); Diseases of the Digestive System and of Metabolism (George B. Eusterman). The authoritative position of the 6 editors should guarantee a wise selection of material, and this is confirmed by perusal of the contents. A wise selection is of especial importance as it is obvious that only illustrative articles on the chosen topics can be treated. A page or more is devoted to each article, liberally interspersed with short editorial notes, so that a good idea can be obtained of the articles' findings and conclusions. By way of illustration, Drs. Minot and Castle start their section with 13 pages (9 articles) on General Considerations; then consider the Macrocytic Anemia (32 articles), Hypochromic Anemias (9), Hemolytic Anemias (11), Hemorrhagic Disease (10), Malignant Neutropenia and Infectious Mononucleosis (8), Leukemia (12 articles). It is obvious that careful reading of such a section would help keep the progressive physician better acquainted with recent advances in hematological fields than would a much longer time spent on perusal of original articles. The danger that he will gradually become content with the mirror rather than the substance should, however, be recognized and avoided by a judicious allotment of available reading time between digests and original articles. E. K.

NEW BOOKS.

Heart Failure. By ARTHUR M. FISHBERG, M.D., Associate in Medicine, Mount Sinai Hospital, New York City. Pp. 788; 25 illustrations. Philadelphia: Lea & Febiger, 1937. Price, $8.50.

Legal Medicine and Toxicology. By THOMAS A. GONZALES, M.D., Acting Chief Medical Examiner of the City of New York; Associate Professor of Forensic Medicine, New York University College of Medicine, etc., MORGAN VANCE, M.D., Assistant Medical Examiner of the City of New York; Assistant Professor of Forensic Medicine, New York University College of Medicine, etc., and MILTON HELPERN, M.D., Assistant Medical Examiner of the City of New York; Assistant Professor of Forensic Medicine, New York University College of Medicine, etc. With a Foreword by HARRISON S. MARTLAND, M.D., Chief Medical Examiner, Essex County (Newark), N. J.; Professor of Forensic Medicine, New York University College of Medicine. Pp. 754; 244 illustrations. New York: D. Appleton-Century Company, Inc., 1937. Price, $10.00.

Physical Diagnosis. The Art and Technique of History Taking and Physical Examination of the Patient in Health and in Disease. By DON C. SUTTON, M.S., M.D., Associate Professor of Medicine, Northwestern University School of Medicine; Attending Physician and Chairman of the Medical Division of the Cook County Hospital, etc. Pp. 495; 298 text illustrations and 8 color plates. St. Louis: The C. V. Mosby Company, 1937. Price, $5.00.

The Story of Living Things. A Short Account of the Evolution of the Biological Sciences. By CHARLES SINGER. Pp. 572; 194 illustrations. New York: Harper & Bros., 1931. Price, $3.00.

A Suggested Experimental Study in Poliomyelitis Prevention Involving the Combined Use of Inactivated Virus and Intranasal Tanning Agents. By S. PESKIND, B.S., M.D. Pp. 7. Cleveland: The S. P. Mount Printing Company, 1937.

Dextrose Therapy in Everyday Practice. A Survey of the Literature, 1900–1936, on the Experimental and Clinical Studies Applicable to Medicine and Surgery. By E. MARTIN, Sc.D., New York. With Forewords by W. N. HAWORTH, F.R.S., Director of the Department of Chemistry, University of Birmingham (Eng.), and BERNARD FANTUS, M.D., Professor of Therapeutics, University of Illinois College of Medicine. Pp. 451; 44 illustrations including 15 full-page plates. New York: Paul B. Hoeber, Inc., 1937. Price, $3.00.

Pathology. By E. B. KRUMBHAAR, M.D., Professor of Pathology, University of Pennsylvania School of Medicine. Vol. XIX of Clio Medica Series. Pp. 206; 18 illustrations. New York: Paul B. Hoeber, Inc., 1937. Price, $2.00.

Gastroscopy. The Endoscopic Study of Gastric Pathology. By DR. RUDOLF SCHINDLER, Associate Clinical Professor of Medicine, University of Chicago; Attending Gastroscopist, Michael Reese Hospital; Consulting Gastroscopist, Cook County Hospital, Chicago. With a Preface by DR. WALTER LINCOLN PALMER, Associate Professor of Medicine, University of Chicago. Pp. 343; 89 text illustrations and 96 color reproductions of gastroscopic observations, with legends. Chicago: The University of Chicago Press, 1937. Price, $7.50.

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PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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MASSIVE COLLAPSE OF LUNG.

MODERN interest in the subject of massive collapse of the lung dates from the work of William Pasteur which was published from 1908 to 1914. Bradford's observations during the war stimulated further investigation and since that time there have been a great many reports from both the clinical and the experimental side. The central problem in the study of massive collapse is that of etiology, but it must be admitted that the answer to this problem is not yet certain, although a considerable amount of data bearing upon the subject has accumulated. In addition to considering the causes of massive collapse, recent investigations have been directed toward determining its incidence and defining the factors which contribute to its occurrence.

In this report only those aspects of massive collapse which have been the subject of recent investigations will be considered. For a complete consideration of the subject, together with its history, the reader is referred to the many excellent reviews on massive collapse, among which may be mentioned those of Churchill,[27] Scott,[122a] Mastics, Spittler and McNamee,[90] Jacobaeus,[73] Brunn and Brill,[22] Band and Hall,[8] Matas[91] and especially, Bowen's extensive monograph.[15]

Definition. Acute massive collapse of lung is the sudden, complete deflation of a considerable part of one or both lungs, in the absence of any rise in intrapleural pressure such as would be caused by pneumothorax, empyema or pleural effusion. This definition has been chosen because it does not arbitrarily rule out any of the suggested causes of massive collapse but does simplify the problem by excluding a large group of cases which might better be called compression of lung.

Clinical Course. Massive collapse of lung is most frequently observed following abdominal operations. The onset of symptoms is sudden; in 80% of cases it occurs within 48 hours of the operation. In a few reported cases the onset has occurred during the operation, and in others it has been several weeks later. Pain, dyspnea, tachycardia and

cough are prominent symptoms. There is nearly always a rise in temperature to 100 to 105° F. The pulse rate is from 100 to 160, and the respiratory rate 30 or more per minute. In the typical clinical case the collapse is unilateral. The chest on the affected side is almost motionless, flat and retracted. The intercostal spaces are narrowed and the percussion note is dull. Over the area of dullness, breath sounds are usually absent, or there may be faint bronchial breathing. Vocal resonance is diminished or absent and râles are rarely heard. The cough is variable; some sputum occurs early in most cases but is never great in amount in the absence of complications.

In unilateral cases the most important diagnostic signs are those indicating a shift of the mediastinum, *e. g.*, displacement of the trachea and of the apex beat.

If the cases are divided into: 1, Acute; 2, moderately severe; and 3, latent, the above description fits Group 2. The acute type may simulate pulmonary embolism with extreme dyspnea and sometimes severe, deep retrosternal pain. A few cases have resembled cardiac infarction. However, most of Groups 1 and 2 more closely resemble pneumonia. In Group 3, the latent cases, there are no symptoms at all, and although the signs are often typical and obvious, they are only found when sought for in a routine examination.

The foregoing description is an attempt to summarize a great many somewhat divergent reports. Many of the details require further discussion. Pain is very variable. Severe pain is rare; some feeling of retrosternal discomfort or constriction is quite common; or there may be no pain at all.[66] Dyspnea is a very common symptom but cyanosis is never severe and is usually absent.[77] Some observers maintain that cough and sputum are nearly always present,[26] others make no mention of them. In tuberculous cases suppression of expectoration is evidently a factor in producing collapse.[66]

In most cases fever of sudden onset has been noted. The absence of fever in some proven cases and in all uninfected cases of experimental collapse suggests that fever may be associated with infection, though in many cases there is no other evidence of infection.

Postoperative massive collapse is usually unilateral. Henderson[62] states that, "as one lung collapses, atmospheric pressure inflates the other lung, hence, massive collapse is almost necessarily confined to one lung; for the collapse of one lung tends to expand the other." Nevertheless undoubted cases of bilateral massive collapse have been reported from clinical observations,[39,96] and bilateral collapse is relatively common at autopsy.[7,12,42b,109a] The clinical course is much the same as in unilateral collapse except that death appears to be a more common result and the diagnostic signs of mediastinal displacement are absent.

Roentgen Ray Appearance. In unilateral cases the important changes observed on Roentgen ray examination are:

1. Increased density of the involved area; 2, displacement of the heart and mediastinum toward the affected side; 3, the diaphragm on the affected side is high and the respiratory excursion is decreased; 4, the intercostal spaces are narrowed on the affected side.

This Roentgen ray picture is identical with that seen in collapse due

to a foreign body in a bronchus. The displacement of diaphragm and mediastinum is never so great in pneumonia or in pulmonary infarction.[65,74,89]

The very great density of the shadow cast by the collapsed lung has been the subject of much speculation. Some report that the lung which collapses spontaneously, as after an operation or the inhalation of a foreign body, casts a denser and more uniform shadow than does a lung artificially compressed by a pneumothorax or consolidated by pneumonia.[132] This difference in density is apparently due to the fact that some air remains in the compressed or pneumonic lung whereas the collapsed lung is completely airless. Van Allen, La Field and Ross[132] have recently emphasized the diagnostic importance of the uniform "ground glass" shadow cast by the collapsed lung. It has also been suggested that the unusual density of the shadow is due to excess fluid in the collapsed lung.[98] For this reason the term "drowned lung" has been applied to lungs which cast this very dense Roentgen ray shadow.

Jacobaeus[73] has called attention to a pendulum movement of the mediastinum which may be the only positive Roentgen ray finding when collapse is slight. This consists of a shift of the heart shadow toward the collapsed side on inspiration and away from it on expiration. Dislocation of thoracic structures is seen at both inspiration and expiration in collapse, but only at inspiration in pneumonia.[132]

Richards[118] emphasized that in typical atelectatic bronchiectasis the collapsed lower lobe is represented by a dense triangular shadow confined to the paravertebral angle and that there is no shift of the mediastinum.

TABLE 1.—REPORTED INCIDENCE OF POSTOPERATIVE MASSIVE COLLAPSE OF LUNG.

Author.	Year.	Reference number.	No. of cases.	No. of operations.	Incidence, %
Pasteur	1914	109*d*	16	2,000	0.8
Pasteur	1914	109*d*	32	3,559	0.9
Scrimger	1921	124	7	540	1.3
Elwyn	1924	42	2	1,734	0.12
Mastics *et al.*	1927	90	32	419	7.6
Scott	1929	122*b*	12	2,000	0.6
Scott	1929	122*b*	7	2,850	0.25
			(Treated with CO^2 postop.)		
Brunn and Brill	1930	22	22	456	4.8
Foss and Kupp	1930	50	2	3,433	0.06
Fuller	1930	51	8	1,478	0.5
Sheret	1930	125	...	149 male	18.1
				112 female	13.7
Brown and Debenham	1932	21	17	812	2.1
King	1933	76*c*	200	7,065	2.8
Eliason and McLaughlin	1934	39	55	26,032	0.21
			32	8,836	0.36
Christopher and Shaffer	1935	26	8	12,494	0.06
Snyder	1935	128	11	1,276	0.86
Rovenstine and Taylor	1936	119	22 partial	7,874	0.30
			13 massive	...	0.20
Watter	1936	136	5	1,455	0.34

Incidence. *Postoperative Series.* The majority of reports concerning the incidence of massive collapse deal only with postoperative cases. The results of these surveys are summarized in Table 1. The extreme variability of the reported incidence is very obvious. It would

appear that the incidence is low (about 0.3%) when routine histories are studied and much higher (3 to 8% or more) when collapse is carefully searched for in each patient following operation. In the latter case, many instances of lesser degrees of collapse are undoubtedly included.

Many other studies of the incidence of postoperative pulmonary complications have been reported in which all complications have been grouped together. In those cases where an attempt has been made to distinguish the various complications, the percentage of complications which have been classed as collapse has varied from zero to 70%. A recent editorial[38] states that, "It appears reasonable to assume from the mass of accumulated evidence that atelectasis is the predominant postoperative pulmonary complication."

Mortality. It is generally agreed that the mortality in clinical cases of massive collapse is low. Scott[122a] collected 40 cases in the literature with no deaths. Many fatal cases have since been reported but apparently no detailed investigation of the importance of massive collapse as a cause of death has been made.

Autopsy Series. In view of the low mortality seen in clinically recognized cases of massive collapse, it is not surprising that there are few reports of the incidence of collapse in routine autopsies. However, consideration of the available data indicates that massive collapse is much more common at autopsy than the clinical reports would suggest. Pasteur[109a] found 2 cases of massive collapse in 55 successive autopsies on surgical cases. A review of the autopsy reports in the Department of Pathology, University of Toronto (1926–35), shows that there were 23 cases of massive collapse in 3346 autopsies in the past 9 years. There were, in addition, many cases listed as partial collapse.

Incidence in Other Conditions. *Hemoptysis.* Massive collapse frequently follows hemoptysis. Mindline[98] has reviewed the reported cases. Jacobaeus[73] emphasized the fact that collapse is most likely to follow a large hemorrhage in a relatively normal lung. Most of the cases occur in tuberculous patients but exceptions to this rule have been reported.[61]

Tuberculosis. The rôle of collapse in the course of pulmonary tuberculosis is attracting an increasing amount of attention. In addition to the cases seen following hemoptysis, many cases of acute massive collapse have been described in tuberculous patients.[52,54,129] It is in these cases that pneumothorax has been most successfully applied in treatment.[43,54,129] Chronic collapse[84] is probably much more common and of greater importance in influencing the course of the disease. Coryllos[30b] regarded collapse as a constant complication of pulmonary tuberculosis. It is generally agreed that collapse exerts a very beneficial influence on the progress of lesions in the collapsed area. This is thought to be due partly to rest and partly to a lowering of the oxygen tension in the collapsed pulmonary tissue.[2,3,30b,71] Cavities which are not in the collapsed area are probably enlarged by the greatly increased negative pressure in the thorax.

Pneumonia. The occurrence of massive collapse as a complication of pneumonia has been frequently reported.[23b,24,32,46,71,90] The view that pneumonia is to be regarded as "an infectious (generally pneumococcic) lobar atelectasis of the lung" has been ably championed by Coryllos and Birnbaum.[14,30a,31a,c] A discussion of the evidence for and against this

view would be out of place here, but it certainly merits careful consideration. If the view proves to be correct, the importance of collapse in pulmonary lesions will be greatly increased.

The relationship of collapse to bronchiectasis is not clear but the two are not infrequently associated.[16,134,135]

Massive collapse has also been reported as a complication of diphtheria,[109a] poliomyelitis, meningitis, bronchitis, child birth,[138] minor injuries, and many debilitating diseases. Its occurrence in cases of asthma will be discussed later.

Factors Affecting Incidence. *Age.* In the 40 cases collected by Scott,[122a] the ages ranged from 12 to 49 years with 40% in the third decade. Eliason and McLaughlin[39] found all ages from 10 to 70 in their series with 19 out of 32 cases between 20 and 40. Watter[136] stated that the incidence of postoperative pulmonary complications in general is proportional to the age of the patient. Others feel that young adults are more liable to collapse.

Sex. In the autopsy series previously mentioned there were 13 men and 10 women. This preponderance of males is generally found. King (see Metcalf[94]) found 38 males in a series of 55 cases, a greater preponderance of males than was found among postoperative pulmonary complications in general. The incidence of collapse in Sheret's[125] series is definitely higher in men. Eliason and McLaughlin[39] found 23 out of 32 cases in men. The difference in incidence has been attributed to the greater effect of pain on the abdominal breather, to which class most men belong.

Infection. 1. *Preëxisting Upper Respiratory Infection.* The importance of preëxisting upper respiratory infections in the causation of postoperative pulmonary complications is emphasized by several authors. Elliott and Dingley,[40] in 1914, noted that all their cases of massive collapse showed fever and mucopurulent sputum before the onset of collapse. Sise[126] found pre-operative respiratory infection in 29% of cases subsequently developing respiratory complications. Sutliffe and Steele[130] have recently reviewed the subject from a bacteriologic viewpoint and conclude that the presence of pathogenic bacteria in the upper respiratory tract does predispose to postoperative pulmonary complications. In an examination of material aspirated from the trachea during anesthesia, Coryllos[30c] found pneumococci in 72% of all cases examined and in 100% of cases which developed postoperative complications. The incidence of massive collapse probably increases along with that of other respiratory complications during the late winter and early spring.[55] This may be related to the increase of respiratory infections at that season.[119]

King,[76b] in an extensive study of postoperative pulmonary complications, concluded that season and pre-operative respiratory infection play a minor rôle in the production of complications.

2. *Infection at the Site of Operation.* The importance of infection at the site of operation in increasing the incidence of postoperative pulmonary complications in general has been pointed out by several workers.[33,120] It is strikingly shown in a series of cases reported by King[76b] in which the incidence of pulmonary complications following simple appendectomy was 6.6% while after appendectomy with abscess formation it was 22.5%.

Site of Operation. Considerable attention has been given to the effect of the site of operation on the incidence of postoperative pulmonary complications.[21,55,76c,119,126] From these papers it may be concluded that complications are much more common after abdominal operations than after any other type and that upper abdominal operations are more likely to be followed by complications, including massive collapse, than are lower abdominal operations. It is interesting that Pasteur[109b] concluded, from his postoperative series, that massive collapse is more likely to follow operations on the lower abdomen. A similar incidence was noted in the autopsy series where 9 of the 14 postoperative deaths followed lower abdominal operations, one followed a gastrectomy and the remaining 4 were after extra-abdominal operations.

Pasteur originally believed that the collapse was almost invariably on the side of the operation. This observation has not been confirmed. In the great majority of clinical cases the collapse has been unilateral but not necessarily on the side of the operation. In the autopsy series 17 out of 23 cases were bilateral.

In a recent review of the occurrence of pulmonary collapse following thoracoplasty, Holst, Semb and Frimann-Dahl[66] found collapse following 51 of 112 operations. In 104 of these cases postoperative Roentgen rays were taken. Since many of the cases were symptomless the incidence would have been much lower if routine Roentgen ray examinations had not been made. In every case the collapse was on the side of the operation. Lambert and Berry[79] found only 6 cases of collapse in 100 patients with 152 operations; in 4 cases the collapse was on the side opposite the operation.

Anesthetic. Many recent investigations have been directed toward discovering the effect of various anesthetics upon the incidence of pulmonary complications in general rather than massive collapse in particular. Without discussing these papers in detail it may be concluded that different anesthetic agents given under similar conditions give rise to approximately the same number of pulmonary complications. Brown and Debenham[21] found respiratory complications 4.29 times as common after spinal as after inhalation anesthetics. Sise,[126] King[76b] and Rovenstine and Taylor[119] failed to find this difference. The latter authors point out the rapid increase in the incidence of complications as the anesthesia is prolonged.

Pre-medication. Dawkins[35] has recently presented evidence for the idea that basal narcosis increases the incidence of postoperative pulmonary complications. Faulkner and Faulkner[45a] have also emphasized the need for rapid recovery from the anesthetic so that the patient can cough up any excess secretion. It is generally agreed that the excessive use of morphine should be avoided. However, small doses probably aid normal respiration by relieving pain, and may even aid bronchial contraction.[23a]

There is considerable disagreement concerning the use of atropine. It seems probable that it should be given pre-operatively, if there is no cough or sputum, to prevent excessive secretion. In the presence of sputum or excessive bronchial secretion, before or after operation, atropine may lead to bronchial occlusion by increasing the viscosity of the secretion.

General Condition of Patient. Rovenstine and Taylor[119] have tabulated the incidence of postoperative pulmonary complications according to the estimated anesthetic risk. The increase in incidence in those classed as C, D or DD risks is very great.

It will be noted that much of the material presented in the foregoing sections deals with postoperative respiratory complications in general rather than with massive collapse in particular. Unfortunately, similar data on collapse do not seem to be available.

Allergy. Considerable attention has recently been given to the possibility that postoperative respiratory complications may be of an allergic nature. Clarke[29] has described the occurrence of typical massive collapse as a complication of bronchial asthma. He states that at least 10% of all reported cases of massive collapse show an allergic history even when no special attention was given to that factor. Wilmer, Cobe and Lee[137] made a detailed investigation of 10 patients who had suffered from postoperative pulmonary collapse and found that all showed some definite manifestations of allergy. They felt that the uniform finding of thick, viscid sputum in cases of postoperative pulmonary complications pointed to an allergic factor. They report good results from the use of peptone for desensitization before operation. The idea that postoperative infarction and collapse are due to an anaphylactic reaction to autogenous polypeptides has recently been advanced in France.[49b] Autohemotherapy for the prevention of postoperative pulmonary complications has been recommended.[75,95]

Before discussing the etiology of massive collapse it is necessary to review briefly some of the recent additions to knowledge concerning the structure and function of the lung.

Pulmonary Musculature. The advent of the bronchoscope and the use of lipiodol have revolutionized the study of pulmonary movements and especially movements of the bronchi. The muscular and elastic tissue found in the lung make free movement possible. The present view is that the muscular coat of the bronchial tree extends right down to the atria[97] or to the alveoli but does not extend into the alveolar walls.[88a,f] Sensory nerve endings are found at the junctions of the bands of bronchial muscle.[53] On the contrary, the elastic tissue of the lung, or arbor elastica, extends from larynx to alveoli, and is continued into the alveoli as delicate strands. In addition to the bronchial musculature, there are many fine wisps of muscle lying outside the walls of the bronchial tree. These filaments are seen in the interlobular septa, in the bronchial and vascular sheaths and in the visceral pleura. The muscle is inconspicuous at any one point but when considered in its entirety it forms an appreciable tissue element in the lung and is known as the insterstitial musculature of the lung.

Bronchial Movement. The movements of the bronchial musculature during respiration may be divided into length changes, width changes and peristaltoid movements. The latter are apparently for the removal of foreign material. The other movements are seen with each respiration. On inspiration, the bronchi not only elongate but also increase in diameter. On expiration, shortening and a decrease in diameter occur.[88a,b,f] The cause of these bronchial movements is not altogether clear. The work of Luisada[86a,b] suggests that there is active contraction and relaxation of the bronchial muscles with each respiration.

Ellis[41] has recently presented evidence to show that the bronchial movements are directly due to movements of the chest wall.

The importance of the length and width changes and peristaltoid movements in the problem of bronchial obstruction is sufficiently obvious to require no comment. The significance of the bronchial and interstitial musculature in relation to collapse of lung is much less obvious. In conditions, such as asthma, in which bronchial spasm is known to occur, emphysema, not collapse, is the usual outcome.

Histology of the Lung. Until recently, pulmonary alveoli have been regarded as sacs opening only into the bronchial tree and lined by a continuous layer of non-nucleated epithelial plates and flattened epithelial cells. Miller[97] has recently reviewed the older literature on the subject and still supports this view. Communications between adjacent alveoli were first described by Adriani in 1847. This observation has been repeated frequently in apparently normal lungs and in pneumonic lungs.[88c,d,106] Miller concluded that these alveolar pores are not normal structures but are due to some pathologic process. Macklin[88d] believed that they are to be regarded as ". . . sharply localized degenerations of the ground substance of the alveolar wall . . ." and of no functional significance. The observations of Van Allen[131] and his colleagues on collateral respiration strongly suggest that some communications exist between adjacent airways in the periphery of the lung.

Not only has the existence of alveolar pores been repeatedly confirmed but considerable doubt has been cast upon the existence of any continuous alveolar epithelium. At a recent conference, where the pulmonic alveolar epithelium was discussed, the majority of observers reported that they had failed to find a continuous epithelium, and none had found non-nucleated epithelial plates.[88c] Miller[97] strongly supports the existence of a continuous alveolar epithelium.

Collateral Respiration. In a series of important papers Van Allen, Lindskog and others have developed the idea of collateral respiration.[82a,b] They found that collapse of lung could not be produced by bronchial occlusion if the bronchus occluded supplied less than an entire lobe. Air forced into a lobular bronchus under very low pressure readily passed out other lobular bronchi in the same lobe. These observations suggested that there must be transfer of air between the lobular bronchi in the periphery of the lung. The injection of India ink and other suspensions showed that this transfer of air was through pores of microscopic size and not by diffusion through intact cellular membranes. This transfer of air from the area supplied by one lobular bronchus to that supplied by another not only serves to maintain the aëration of the lung when a lobular bronchus is occluded but also prevents local overdistention if a valvular occlusion occurs. This mechanism also provides the air necessary for an expulsive effort on coughing when a bronchus is occluded.

The existence of collateral ventilation seems to be well established, in the dog at least. The amount of air which can enter an occluded lobule is at least 10% of its normal ventilation and may be sufficient to aërate the venous blood in that part of the lung. The significance of collateral respiration in relation to pulmonary collapse will be discussed below.

The Expansion of the Lung. Under normal conditions, the lungs are subjected to two opposing sets of forces. Atmospheric pressure, acting through the bronchial tree, tends to keep the lungs expanded and in contact with the chest wall. The elasticity of the lung and the intrapleural pressure oppose this force and tend to collapse the lung. Normally the sum of pulmonary elasticity and intrapleural pressure is just less than atmospheric pressure so that the lung is kept expanded. Thus the amount by which the intrapleural pressure falls short of atmospheric pressure is a measure of the force required to stretch the lung to fill the thorax.

There are three ways in which a part of the lung can collapse. These are: 1, Increase of matter other than lung in the thorax (*e. g.*, pneumothorax, hemothorax, empyema, pleural effusion, tumors); 2, decrease in the size of the thorax due to decrease in muscle tone or localized paralysis affecting any of the respiratory muscles; 3, forceful decrease in the size of the lung: (*a*) due to absorption of air from a part of the lung that has been cut off from the outside; (*b*) due to active muscular contraction of the lung.

It is obvious that in the first and second groups the intrapleural pressure will be less negative than normal because the lung is less stretched. In the third group, part of the lung has been decreased in size so that the remaining lung has to be stretched more than normally to fill the thorax. This results in a decrease in the intrapleural pressure.

By definition all cases of massive collapse have been placed in the third class and there is good evidence, both direct and indirect, that this classification is justifiable. In all reported cases of massive collapse in which the intrapleural pressure has been measured it has been below normal.[43,54,57,72] The lowest reported pressure is −58 cm. of water.[84] Indirect evidence for this decrease in intrapleural pressure is given by the uniform finding of a shift of the mediastinum to the affected side.

The Effect of Operations upon Respiration. Since abdominal operations are the most common cause predisposing to massive collapse, a knowledge of the effects of operation upon respiration is necessary before considering the etiology of massive collapse.

By combining the observations of many workers the following picture of the patient's pulmonary condition after an abdominal operation is obtained. The mean position of the diaphragm is raised so that its tidal excursion is in the upper third of its range instead of the lower third as is usual.[103] Chest expansion decreases by about 80% and diaphragmatic excursion by 65% following upper abdominal operations.[103] These changes result in a decrease in vital capacity of 8 to 80%.[25,28,110] Vital capacity measurements are not very reliable after operation but measurement of the subtidal volume (mid-capacity, functional residual air, etc.) which are more significant show a decrease of 20%.[10] Many cases show Roentgen ray changes including haziness of lung fields, prominence of basal trunks and elevation of the diaphragm. Diminished expansion of the lung bases is said to occur in all cases after operation. Breath sounds are diminished or absent at the bases in most cases and râles are frequently heard.[103,108]

Many factors contribute to these pulmonary changes. Pain definitely limits respiratory movements. Air in the peritoneal cavity increases the normally negative intraäbdominal pressure and contributes

to the elevation of the diaphragm. Distention of the bowel may add to this effect. Henderson[62c] has recently emphasized the importance of the general loss of muscle tone seen after operations. Decrease in tone of the respiratory muscles diminishes the size of the thorax and the extent of respiratory movements.

The vital capacity of a normal individual is reduced by 10 to 20% by merely changing from the erect to the supine position.[19,68] If this position is maintained, deflation of the lung bases follows. Thus position probably contributes to the postoperative pulmonary changes.

The condition of the lungs described following operation has been called postoperative pulmonary sub- or hypoventilation.[115] It is distinguished from massive collapse by the fact that the intrapleural pressure is increased, while it is always diminished in massive collapse. In addition, pulmonary subventilation is bilateral and is associated with an enlargement of the diameter of the thorax.

Etiology. Of all the suggested causes of massive collapse of lung, bronchial obstruction is the best established. Mendelssohn, in 1845, showed that complete occlusion of a bronchus resulted in collapse of the lung distal to the occlusion. Lichtheim, in 1878, showed that this collapse was due to absorption of the retained air into the blood. Elliott and Dingley[40] first clearly suggested that bronchial occlusion is essential to the production of postoperative massive collapse. The introduction of the bronchoscope has thrown much new light on the problem of bronchial obstruction in recent years. Direct observation has revealed the presence of occluding secretion in the bronchi in many cases of massive collapse.[20,22,59,60,69,70,105,127]

The more important evidence favoring bronchial obstruction as the cause of massive collapse may be summarized thus:

1. Massive collapse has been repeatedly produced experimentally by bronchial occlusion, whether the occlusion was produced by ligation of a bronchus,[92,131] introduction of solid foreign bodies,[116] or tenacious bronchial secretion,[8,80] or by cauterizing a bronchus.[1,34] This is the *only* way in which massive collapse has been produced experimentally. Much has been learned concerning the circulatory and metabolic changes which follow the experimental collapse of a lung by bronchial occlusion.[4,6,31b,37]

2. Massive collapse is seen clinically following occlusion of bronchi by foreign bodies, neoplasms, aneurysms, or enlarged lymph nodes. The Roentgen ray picture and clinical signs in this type of collapse may be indistinguishable from those of postoperative collapse.[89]

3. Bronchoscopic observations have shown that the bronchi supplying a collapsed lobe are frequently occluded by plugs of tenacious bronchial secretion. Removal of these plugs usually results in rapid reëxpansion of the collapsed lobe.

4. Collapse is commonest in the right lower lobe where secretion or aspirated material is most likely to collect. Cases with excessive bronchial secretion are very likely to develop collapse. The areas of collapse may shift with the position of the patient, suggesting a movement of exudate within the lungs.[44a,b,45a,b]

There is some disagreement among the proponents of the bronchial obstruction theory concerning the cause of the obstruction in postoperative collapse. In cases of collapse following aspiration of a foreign

body, hemoptysis or lipiodol injection, the cause of obstruction is obvious. After operations, obstruction is most likely caused by accumulation of bronchial secretion. Several factors may contribute to the accumulation of secretion. Pulmonary subventilation, resulting in diminished movement at the lung bases, leads to deficient drainage of those regions. "Internal drainage"[44a,b,45b,85] may bring secretion from other parts of the lung to the most dependent areas. Postoperative shock[99,100] and vagal stimulation[112] may result in an increase in bronchial secretion or even some degree of pulmonary edema. At one extreme may be placed cases in which excessive interference with lung movements results in the accumulation of normal bronchial secretion. At the other extreme are cases such as hemoptysis in which an excessive amount of fluid may occlude bronchi in the presence of normal respiratory movements.

Faulkner and Faulkner[45a] suggest that aspirated material may be an important cause of bronchial occlusion. Myerson's direct bronchoscopic observations, which showed aspiration of blood into the tracheobronchial tree in 79 out of 100 tonsillectomies, support this view.[104]

Other suggested causes of bronchial obstruction are inflammatory edema of the bronchial mucosa, vascular changes[123] in bronchi, possibly analogous to angioneurotic edema,[12] and bronchial spasm.[42,81,111] Inflammatory edema would appear to be the cause of collapse in cases of atelectatic bronchiectasis[134,135] but has not been demonstrated in cases of acute massive collapse. There is little evidence for the occurrence of angioneurotic edema. There is no direct evidence that bronchial spasm alone can produce pulmonary collapse. In conditions associated with bronchial spasm, emphysema is more likely to occur than collapse. Recent reports of the high incidence of an allergic history[137] in patients suffering from postoperative pulmonary complications and of the occurrence of true massive collapse in asthmatics[29] suggest that bronchial spasm may be an important contributory cause. The work of Dixon and Brodie[36] shows that bronchial spasm combined with a greatly decreased ventilation (artificial respiration) may result in the rate of air entry to a lobe being less than the rate at which the blood is absorbing air from that lobe, so that the lobe slowly deflates.

Collapse of lung following bronchial obstruction might arise either from a ball-valve action of the obstructing plug so that the air is pumped out of the obstructed lung, or from absorption of the air beyond the plug into the blood stream. The possibility of the latter mechanism has been repeatedly demonstrated.[31b,63] The impossibility of the deflation of a part of a lung by ball-valve action has been clearly proven by Lindskog and Van Allen.[83]

The important evidence against bronchial obstruction as the cause of massive collapse is:

1. At autopsy, patent bronchi are frequently found in collapsed lung. It is suggested that the occluding plugs, in these cases, have undergone postmortem liquefaction or that the occlusion is in smaller bronchioles. Clinical findings (*e. g.*, tubular breathing) sometimes suggest patent bronchi in collapsed lobes. In a few cases, bronchoscopic examination has failed to reveal any plugging of the bronchi.[20,22]

2. Rose Bradford's[17] observations on massive collapse following thoracic injuries are of great interest. He found that massive collapse

was a relatively common sequel to chest wounds seen during the war. The collapse might involve part of a lobe, a whole lobe, or an entire lung. In some cases, the collapse was on the side of the injury, in others on the opposite side and a few were bilateral. The most striking cases were those in which a non-penetrating wound of the thoracic wall resulted in massive collapse of the contralateral lung. Bradford feels that bronchial obstruction played no part in these cases.

3. Several cases of rapid collapse of the lung have been reported in which the apparent rate of collapse greatly exceeded that which could be due to the absorption of air.[12,73,81b,111] In some of these cases the rapid collapse may have been due to the rapid absorption of ether vapor rather than air from the lungs. Jacobaeus[73] reports 4 cases in which massive pulmonary collapse developed within 10 to 15 minutes following the injection of lipiodol into normal lungs without anesthesia. He suggests that the collapse was due to bronchial spasm which expelled most of the air before occluding the bronchi. The amount of lipiodol used was apparently not enough to occlude the bronchi, and the collapse often occurred in lung areas in which there was very little lipiodol and the collapse disappeared without the expectoration of lipiodol. Mindline[98] believed that collapse following hemoptysis is due to the same cause. In all these cases it seems to be impossible to be sure that bronchial obstruction was not present, but the rapidity of collapse cannot be explained by the absorption of air. Lubin[85] suggested that very rapid collapse follows bronchial occlusion in expiration.

4. Cases of collapse following tracheotomy have been noted.[139] These would appear to be due to an actual contraction of an unusually elastic lung. There is no suggestion of bronchial obstruction.

5. The finding that the areas of collapse often do not follow lobar boundaries cannot be reconciled with the observations on collateral respiration, if the collapse is due to bronchial obstruction, unless it is supposed that the alveolar pores are often occluded.

6. Some of the clinical signs of massive collapse, such as fever, are not duplicated in experimental collapse produced by bronchial occlusion. It seems probable that the presence of infection is necessary for the production of fever and that fever is not due to the collapse of lung. However, there are many clinical cases in which the fever is the only sign of infection.

This discussion shows that the theory of bronchial obstruction as the cause of massive collapse is not entirely satisfactory, and yet there is no substitute for it.

Briscoe's[19] theory that the symptoms of massive collapse are always due to an associated acute pleurisy and never to the collapse of the lung has received no support.

Embolism has never been shown to cause collapse and the two are rarely associated. It has been shown that ligation of the one pulmonary artery does result in partial deflation of the affected lung but never in a true collapse.[101] It appears that the arterial blood pressure normally aids in maintaining the inflation of the lung. Vascular changes other than embolism have been suggested but have never been accurately defined.[12,123]

Massive collapse, like most other conditions, has been blamed on reflex causes. It seems certain that inhibition, probably reflex in origin, of the diaphragm and other respiratory muscles is an important contributing factor. Collapse has never been produced by nerve stimulation and has been seen to occur in the denervated lung.[48]

Pasteur has adhered to the opinion that decreased respiratory force is the prime cause of massive collapse. The arguments against this view are: 1, If decreased respiratory force were the cause of collapse, the intrapleural pressure would be increased when collapse occurs. It is always decreased; 2, if decreased respiratory force could cause unilateral collapse, the heart would be shifted to the side opposite the lesion. Decreased respiratory force, leading to pulmonary subventilation, is generally believed to be a most important factor in favoring accumulation of secretion, bronchial occlusion and massive collapse, but it cannot be admitted as a cause of collapse *per se*.

This discussion leaves active contraction of the lung and bronchi as the only theory to oppose that of bronchial obstruction. Recent work has shown that the lung is a very muscular organ but it has not proven that contraction of this muscle can expel the air from the lungs or even completely occlude bronchi.

Prevention of Collapse. The factors which seem to be effective in controlling the incidence of pulmonary collapse after operation can all be deduced from the causes which are known to contribute to the occurrence of collapse.

Except in emergencies, patients with upper respiratory infections should not be operated upon. Care must be taken to avoid all aspiration during the anesthetic. Recovery from the anesthetic should be rapid and postoperative sedation should be carefully controlled. Too much morphine depresses respiration and favors the accumulation of bronchial secretion. Too little morphine may result in limitation of respiratory movements by pain. Small doses of morphine may actually increase bronchial motility.[23a]

The use of atropine has been widely discussed. At present, it is generally agreed that excessive doses of atropine make the bronchial secretion tenacious and favor occlusion. It is best used only when bronchial secretion is excessive. Pasteur[109d] reported favorably on its use. Expectorants are often recommended to thin bronchial secretion.

Abdominal dressings should be small and loose. The patient should be rolled frequently to avoid stagnation of secretion in one part of the lung.[121] Complete expansion of the lungs should be induced at least every hour by voluntary deep breathing combined with rolling or by the use of carbon dioxide.

The inhalation of carbon dioxide has been widely used for the prevention and treatment of collapse and of postoperative pulmonary complications in general. The action of carbon dioxide in increasing the rate and depth of respiration is too well known to require discussion. It has been shown experimentally that carbon dioxide causes bronchodilatation,[18] an increase in mean thoracic girth and expansion[13] and a decrease in intrapleural pressure. Bronchoscopic observations show that carbon dioxide inhalation produces violent movements of the tracheobronchial tree and blanching of the mucous membrane.[20,22]

There is less reduction in vital capacity after abdominal operations if carbon dioxide is given.[113]

Although all these actions of carbon dioxide would appear to be beneficial in preventing postoperative pulmonary complications, opinion is divided concerning its value. The majority of workers reporting on the subject favor the use of carbon dioxide.[22,26,44b,47,62b,87,122b,128] In most cases it is stipulated that the inhalations must be combined with postural drainage. Others[76,120,136] find that carbon dioxide inhalations are without value for the prevention of postoperative pulmonary complications. Reports of the use of carbon dioxide in the treatment of pneumonia are very encouraging.[56,64] In general, it would appear that the administration of carbon dioxide in amounts adequate to produce real overventilation combined with postural drainage is beneficial.

Treatment of Collapse. The measures which have been advocated for the prevention of collapse (*i. e.*, rolling, deep breathing, and carbon dioxide administration with postural drainage) are also used in treatment of the established condition. In addition, bronchoscopy for the evacuation of retained secretion has been extensively used in treatment.[20,22,39,44b,49,59,60,105,127] The results of bronchoscopic aspiration are usually beneficial and relief of symptoms and reëxpansion of the collapsed lung occur with dramatic rapidity. In a few reported cases no bronchial occlusion adequate to explain the collapse present could be seen with the bronchoscope. Bronchoscopy has even been recommended pre-operatively in cases showing excessive bronchial secretion. Excellent results have been reported using endotracheal anesthesia with bronchial suction during operation.[30c]

The use of pneumothorax for the relief of symptoms due to the displacement of the mediastinum was formerly advocated but does not seem to have been much used in recent years.[9,40,43,54,72,98]

Breathing air under positive pressure has been shown to reëxpand collapsed lung experimentally[82] and has also been used clinically.

In so far as a study of the successful methods of prevention and treatment of collapse sheds any light on the etiology of the condition, it supports the idea that collapse is due to bronchial occlusion by retained secretion.

Summary. Massive collapse of lung is most likely to occur under conditions where respiratory movements and bronchial drainage are interfered with and vital capacity is reduced. The constant finding of a decrease in the intrapleural pressure on, and a shift of the mediastinum toward the side of the collapse proves that there must be an active diminution in the thoracic contents on that side. Such a decrease could result only from absorption of air following bronchial occlusion or from expulsion of air by active contraction of lung. The balance of evidence favors the view that the collapse is due to bronchial occlusion. Certain cases of rapid collapse cannot be explained on this basis and may be due to actual contraction of bronchial and pulmonary musculature. An allergic factor may be important in some cases. The bronchial obstruction theory serves as a reliable guide to prevention and treatment.

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HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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TRICHINOSIS: AN UNSOLVED PROBLEM IN THE UNITED STATES.

In a series of articles recently appearing in the Public Health Reports of the United States Public Health Service it has been stated that this country has the greatest problem in trichinosis of any country in the civilized world and that the efforts to control this infection during the past two or three decades have brought about little if any reduction.

Frequency of Infestation in Man. Satisfactory estimates of the frequency of the infection of man with trichinæ can only be obtained by the examination of bits of muscle tissue removed postmortem. Hall and Collins[4] have recently completed observations on specimens from 300 diaphragms removed at autopsy from patients dying in 10 hospitals located in Washington, D. C., and one in Baltimore, Md. Since 5 of these hospitals cared for Federal beneficiaries sent from all over the United States and since the population of Washington, D. C., is to an unusual degree drawn from various parts of the country, they believe the sample, though small, to be fairly representative.

The diaphragms were examined for trichinæ by the direct microscopic method and by the digestion-Baerman method. The supplementary value of the second procedure was demonstrated by adding half as many positives again as would have been revealed had direct examination alone been used. In all, 41 of the 300 diaphragms were found to be infected with trichinæ, a frequency of 13.67%.

Including their own observations with those of previous writers who had made similar studies in different parts of the United States there are available in the literature 1778 observations made upon postmortem material. Trichinæ were found in 222 (12.5%). Hall and Collins point out that this percentage cannot be taken on its face value as an average or as an index, on account of the limitations of the methods of examination, the relatively small numbers, and the limited geographic area represented. They are inclined to believe that the percentage is too low rather than too high.

Magath,[7] on the other hand, has pointed out that only 5 of these studies were made during the last 35 years, and that the material was obtained very largely from bodies examined at necropsy in charity hospitals or from cadavers on dissecting tables in medical schools. It represented, therefore, to a considerable degree those who are down and out, who live from hand to mouth and of necessity eat inferior and poorly prepared food of all sorts.

Magath himself, however, brought further confirmation to the estimate of Hall and Collins. He examined muscles from the bodies of 220 patients who had died of various causes at the Mayo Clinic. This

clinic draws its patients widely from the United States and very largely from the upper income brackets. Two grams of muscle from the diaphragm, the intercostals, the rectus abdominis and the sternocleidomastoid were compressed and searched with a binocular microscope. Trichinæ were found in 17 bodies (8%). Magath thought that it was safe to assume that the actual incidence of infection in this series would have been 12 to 15%, had the direct examination been supplemented by a digestion method or 50 to 100 gm. of muscle examined.

Admitting the desirability of more extensive observations over a wider geographic area, the data at present available in the United States indicate that trichinæ are found in the muscle tissue of approximately 1 out of every 8 persons at the time of death.

Frequency of Clinical Trichinosis. Of the 41 positive cases found by Hall and Collins none had any previous history of clinically recognized trichinosis, so far as could be ascertained from routine clinical histories taken during their last hospital admission. Yet in one of the cases there were between 900 and 1000 trichinæ per gram of diaphragm muscle. In the 17 cases discovered by Magath at the Mayo Clinic, with exceptionally complete and accurate records, only 7 gave a history of symptoms suggestive of infection, but these were readily explained on the basis of other conditions found. In not a single instance in either series had the diagnosis of trichinosis been established before death.

The occurrence and severity of symptoms are largely determined by the number of trichinæ, their organ distribution, the rapidity of the invasion and the resistance, natural or acquired, offered by the tissues of the host. So far as numbers are concerned, Hall and Collins[4] think that it is safe to say that in infestations with over 100 larvæ per gram there must be pronounced clinical symptoms. In infestations with less than 1 larvæ per gram symptoms are either absent or neglible. Sufficient data are not yet available to permit more accurate statement of the clinical threshold. Enough evidence is available however, to state that the vast majority of individuals who acquire infestations with this parasite are unaware of its presence in the body and suffer no appreciable handicap therefrom. In a small proportion which the figures of Hall and Collins would suggest to be about 1 in 20, the distribution and intensity of the infestation is of sufficient degree to cause considerable damage to the host and to produce symptoms which are sufficiently characteristic to permit clinical recognition.

Ransom[9] found that among the 1550 cases reported in the United States from 1842 to 1915, there were 240 deaths, a case fatality rate of about 16%. Since the reported cases would tend to be weighted to an unusual degree by severe infections, this rate is only an approximation and probably higher than would be found if all clinically recognizable infections were included. It can only be used with this reservation.

Implications of the Data. By applying the ratios obtained in these studies to the population of the United States, Hall and Collins conclude that "the problem (of trichinosis) is one of major importance, apparently affecting, to some degree, as a conservative estimate, several million persons, with clinical trichinosis in some form affecting possibly several hundred thousand persons, and with possibly several thousand deaths."

Even granting that the rates obtained from these very small samples are representative of the whole population of the United States, one

might question whether these statistical inferences are permissible. The frequency of infestation was based upon persons who had died, and not upon persons who were living. The encysted trichinæ which were found, in many instances dead and calcified, had been introduced into the tissues some months or years previously, or represented the cumulation of repeated doses over a long period of years. One cannot infer, therefore, that the frequency of finding trichinæ postmortem is synonymous with the incidence of the infection in the living.

Again, the age distribution of persons who have died is not the same as the population who are living, and Hall's[3a] data indicate that the frequency of infestation varies with age, being lowest during the first two decades of life.

By analogy, even though 50% of persons show evidence at postmortem of a healed focus of tuberculous infection, to infer from this that 50% of the population are suffering from tuberculosis is obviously misleading. It can only be inferred that at least 50% at the time of death have been infected with tuberculosis sometime during life.

With these considerations in mind, it would seem to be more nearly in accord with the ascertained facts to state that as high a percentage as 12.5% of the 1,400,000 persons who die each year in the United States (175,000 persons) may show evidence of having acquired an infestation with trichinæ at some time previous to death, and that, in perhaps 1 out of 20 of these (8750) the infestation was sufficiently severe to cause symptoms. Assuming in the latter group the case fatality rate to be as high as 16% (Ransom), 1400 of these deaths might have been caused by this parasite, as a liberal estimate.

Stated on this basis there is still reason for agreeing with Hall and Collins that exposure to infestation with trichinæ is far more frequent than is commonly realized, that morbidity and mortality reports fail to indicate the real extent of the problem, that a considerable proportion of infestations which are clinically recognizable, and even of deaths due to this cause, escape recognition.

Clinical Recognition. In a paper on "The Complex Clinical Picture of Trichinosis, and the Diagnosis of the Disease," Hall[3b] maintains that the most serious gap in our knowledge of trichinosis, so far as medical practice is concerned, is our ignorance of the clinical picture. The question might be raised whether it is so much a matter of ignorance of the clinical picture, which has been very fully described by numerous medical writers during the past 50 years, as it is a matter of failure to suspect such a cause of illness because of its (supposed) rarity, and because the symptoms presented in a large proportion of cases are so irregular and protean in character as to render differentiation from other disease conditions difficult or impossible without the aid of a specific diagnostic test.

When a group of individuals are infected at the same time, as in the family reported by Otto and Janney,[8] and the epidemic reported by Drake, Hawkes and Warren,[1] sooner or later the diagnosis will probably be suspected, particularly if the affected group are of foreign extraction and if a definite history of having eaten raw, partially cooked or insufficiently processed pork products can be obtained. Even when the epidemiologic evidence of the nature of the illness is strong, it is not easy to establish the clinical diagnosis with certainty, and when cases occur singly or sporadically this difficulty is augmented.

The value and limitations of laboratory aids—particularly the differential blood count (eosinophilia), the biopsy, the skin test and the precipitin test—have recently been discussed by Friedlander,[2] Spink and Augustine,[10] Heathman,[5] Kaljus,[6] Magath,[7] and Hall.[3b] When negative, they are of no value. When positive, the difficulty is in distinguishing between a reaction due to acute trichinosis, *i. e.*, the stage of invasion—and one due to an invasion which took place months or years before and has since become latent and healed.

After reviewing these discussions, one can only agree with Hall[3b] that more accurate and specific tests for the diagnosis of acute trichinosis are highly desirable, but, after diagnosis, what? Possibly in the future some usefully chemotherapeutic measure will be developed. On the basis of present knowledge the problem is one of prevention.

Control. To dismiss the problem of prevention by stating that there is still need for emphasizing the importance of cooking pork thoroughly before it is consumed, is somewhat analogous to an attempt to control milk-borne disease by advising the general public not to drink raw or improperly pasteurized milk. Moses recognized the human limitations to such advice some two thousand years ago, and forbade the eating of pork.

Aside from this gratuitous advice, the present control program is limited mostly to Federal supervision of the refrigeration and processing of those pork products customarily eaten without cooking. "Unfortunately, almost one-third of our meat supply comes from houses not shipping in interstate commerce and therefore not under Federal inspection or an equivalent inspection; and as sold or as served in public eating places, uninspected pork products are shuffled, indistinguishably, with inspected products, some places selling or serving inspected, and others uninspected products."[3c] Moreover, as Hall would be the first to admit, the inspection of hogs, even as carried out under the direction of the Federal Bureau of Animal Industry, does not, and has not for many years, attempted, nor claimed that it could, eliminate trichinous pork. It has only decreased the exposure and dosage, by improving methods of processing, *i. e.*, refrigeration, smoking, curing, and so forth, of pork products.

The prevention of human trichinosis rests in the last analysis upon control of the disease in swine. Hall[3c] estimates that the incidence of live trichinæ in swine over the country as a whole is between 1 and 2%. This incidence will vary, apparently from 0% in swine raised under the swine-sanitation system, through a small fraction of 1% in Southern swine and 1.5% in grain fed swine, to between 4 and 5% in garbage-fed hogs. Furthermore, he states that the status of trichinosis in these groups of swine has not changed materially in the past 50 years.

He believes that the parasitic cycle of trichinosis in hogs is maintained by swine eating pork scraps in garbage containing encysted larvæ, supplemented to a small and insignificant degree by swine eating the remains of infected rats. Hence, he reasons that to the extent that pork scraps are excluded from garbage, or better, to the extent that garbage-feeding is discontinued, trichinosis will decrease and disappear. Moreover, he states that there are reasons for believing that garbage feeding is economically unsound. If his premises are correct, then there is no insuperable obstacle in the way of control. In fact, one

might ask why the Federal Bureau of Animal Industry, the packing industry, and the swine-raising industry have not made progress in this direction during the past 40 years. The preventive problem is veterinary rather than medical, and from the human point of view an important one.

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